Treatment Outcomes with Osseointegrated Brånemark Implants in Diabetic Patients: A Retrospective Study

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
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Abstract:

All diabetic patients treated with Brånemark osseointegrated implants in the Implant Prosthodontic Unit of the Faculty of Dentistry, University of Toronto were identified by way of a retrospective chart survey. Each of these patients was matched to two control subjects by age, sex, location of implants (jaw and zone), type of prosthetic restoration, opposing arch and duration of edentulism. Additional factors including the presence of other medical conditions, smoking habits, medication use, and bone quality and quantity of the jaw treated with implants were controlled for by utilising logistic and linear regression.

Diabetic patients had no increased risk of implant failure, lost more bone in year one of loading, had less soft tissue complications, had a similar numbers of prosthodontic complications and reported more paresthesia and less post operative pain compared to matched non-diabetic controls.

These results suggest that non-brittle diabetic patients should be considered for treatment with implant supported prosthesis.
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Introduction:

Brånemark implants have been used successfully in clinical dentistry for the past thirty years. Numerous studies have reported clinical outcomes of this modality in both edentulous as well as partially edentulous patients. (Zarb and Schmitt 1990a,b,c, Avivi Arbor and Zarb, 1996; Wyatt and Zarb, 1998)

The small percentage reported of early implant failures has been generally regarded as being the result of flawed site selection, aggressive surgical technique or movement of the implant due to early loading. Late failures, although relatively rare, have variously been reported as resulting from occlusal overload; i.e. a functional loading which exceeds the bearing capacity of the surrounding bone (Isidor, 1997) or as a result of bacterial infection. (Mombelli et al, 1987)

While most authorities concur that overload is certainly a factor, a controversy surrounds the role played by the periodontal pathogens. Several authors have reported that their presence in certain individuals leads to greater bone loss and hence earlier loss of the implant while others have held that their role is minimal in the recorded late failures.

Other factors such as smoking, (Bain, Moy, 1993, Lindquist et al, 1997, Habsha, 1998) cardiovascular disease (Khadiivi, 1993), age (Bryant, Zarb, 1998), osteoporosis (Dao, Anderson and Zarb, 1993), medical health and medications (Weyant, 1994), and estrogen levels (Cuerin, 1997) have also been investigated with respect to their role in the treatment outcome of osseointegrated implants. However with the exception of smoking (Lindquist et al, 1997) these factors have not been investigated with respect to their role in the behaviour of the marginal bone surrounding implants with time.

Reported data on the behaviour of the marginal bone surrounding Brånemark implants suggests that some patients experience bone loss which exceeds the 0.1 mm. annual rate reported
for the majority of sites, but do not suffer implant loss in the short term. In addition other patients may even experience bone growth around their implants. (Wyatt, 1996) In a prospective study, Wyatt reported that approximately 15% of the patient population experienced bone loss exceeding 0.1mm per year and that 15-20% had bone growth. He observed no link with age, sex, or the presence of marginal inflammation after the first year. He reported that bone loss around implants was not affected by the existence of gingival inflammation. He did find however increased bone loss around implants placed in younger patients, in males, in patients with implant supported distal extension prostheses and in the mandible when compared to the maxilla in the first year of loading. His study did not attempt to identify systemic or behavioural factors impacting on the physiology of the bone surrounding implants (Wyatt, 1996, Wyatt and Zarb, 1997).

Lindquist et al (1997) recently reported on the association of smoking and marginal bone loss in a 10 year follow-up study. They found that more bone loss was observed in smokers when compared to non-smokers, and that poor oral hygiene combined with smoking caused a further increase in the bone loss observed. Poor oral hygiene in non-smokers had little effect on the bone loss pattern. Since there is little research on the wide spectrum of factors, which may impact on peri-implant bone behaviour, it seems prudent to begin to focus on these factors. A partial list of these factors would include:

(a) general health conditions such as diabetes, cardiovascular disease, kidney disease, allergies and hypertension;

(b) medications such as estrogen, progesterone, NSAIDS, steroids, diuretics and antibiotics and

(c) social behaviors such as a stressful lifestyle and/or stressful events and alcohol consumption.
While a lack of factor/bone loss studies is evident in the implant literature, the periodontal literature also provides much information about the factors influencing bone loss surrounding natural teeth and may provide clues regarding bone behaviour surrounding implants. Higher rates of bone loss around natural teeth with periodontal disease have been estimated at between 7-15%; which is not different from that seen around implants. Bone loss has been found to vary with many factors including various bacterial pathogens, systemic health and medications taken. For example the rate of bone loss has been found to increase with diabetes (Thorstenson, 1995, Taylor et al, 1998), stress (Moss et al, 1996), alcohol use and smoking (Grossi et al, 1995), and to reduce with the use of tetracyclines (Golub et al, 1994), NSAIDS (Feldman et al, 1983), a history of kidney disease (Grossi et al, 1995), and allergies (Grossi et al, 1995). Furthermore, the medical literature suggests other factors, which play a role in bone metabolism. thyroid hormone therapy (Schneider et al, 1994, Uzzar et al, 1996), estrogen therapy (Sowers et al, 1993), low dose glucocorticoid therapy (Saito et al, 1995) and thiazide therapy (Morton et al, 1994, Feskanich et al, 1997) have all been shown to influence the behavior of bone.

It is tempting to speculate that those factors identified as having an effect on the bone behaviour around natural teeth in both periodontal disease and during periodontal therapy will affect the circum-implant tissue in a similar manner, however, this remains mere speculation and demands verification by research. Given the breadth of this list of factors, it seems prudent to narrow the scope of the initial study to focus on one factor, which impacts on a relatively large number of patients. It also seem advisable to select a factor which has been widely reported in both the dental and medical literature with respect to its effects on systemic physiology as well as with respect to its more specific effects on the oral tissues, and on wound healing. I propose therefore to focus on Diabetes mellitus.
Diabetes mellitus is a widespread metabolic disorder which affects 4-5% of the population and accounts for 25% of end stage renal failures, 50% of all lower extremity amputations, is the leading cause of blindness and accounts for 10% of patient days in the hospital. (Andreoli et al, 1990). It presents in three distinct forms; juvenile onset, insulin dependant diabetes mellitus (formerly known as IDDM, now identified as Type 1); maturity-onset, non-insulin dependent diabetes mellitus (formerly known as NIDDM, now identified as Type 2); and diabetes during pregnancy (Gestational Diabetes, GDM). In addition, numerous other uncommon conditions associated with various genetic disorders, disease states or drug usage are associated with the development of a diabetic state and are classified under the broad heading “Other”. Type 1 is an organ specific autoimmune disease and a genetic predisposition appears to exist for it. Type 2 on the other hand has an autosomal dominant inheritance pattern with onset being triggered by environmental factors; specifically obesity. Diabetes is characterised by hyperglycaemia, glucosuria, polyuria, polydipsia and polyphagia and is associated with both acute and chronic complications as a result of altered fat, protein and lipid metabolism. Among the acute complications are ketoacidosis, and non-ketotic hyperosmolar syndrome. Chronic complications include atherosclerosis, arteriosclerosis, coronary artery disease, microangiopathy, retinopathy, blindness, nephropathy, susceptibility to infections and delayed wound healing (Guyton, 1987).

Considerable research has been conducted concerning the impact of diabetes on the incidence, the progression and the pathogenesis of periodontal disease. Diabetes’ impact on the immune system; both at the humoral (Claggett and Page, 1978, Anil et al, 1990(a), 1990(b), 1990(c)) and cellular levels (Manouchehr-Pour et al, 1981, Nicolo et al, 1989, Cutler et al, 1991); on collagen metabolism (Kaplan et al, 1982, Ramamurthy and Golub, 1983,) and on the micro-
circulation (Frantzis et al, 1971, Listgarten et al 1974,) has been investigated. Diabetes is known to modify and to aggravate the severity of periodontal disease. Diabetics with early onset, long duration and a brittle control outcome are more susceptible to periodontal disease. They have more signs and symptoms such as increased gingival inflammation, increased bone loss, increased attachment loss and deeper periodontal pockets (Belting et al, 1964, Glavlind et al, 1968, Cohen et al, 1970, Hugosan et al 1989, Taylor et al, 1998) than the non diabetic patient. They have also been shown to have delayed healing responses to surgery and less favourable surgical results. (Bashkar, 1986, Fahey et al, 1991, Devlin et al, 1996,).

Despite the fact that much work has been done in the field of periodontology and medicine with respect to the impact of diabetes, very little research has been done with respect to its impact on the success/failure picture of oral implants or its impact on the metabolism of the peri-implant tissues of gingiva and bone. Several studies have included diabetics in their treatment groups (Mericske-Stern and Zarb, 1993), yet only four studies (Smith et al, 1992, Shernoff et al, 1994, Kapur et al, 1998, Balshi et al, 1999) have specifically examined the role of diabetes in the success or failure of oral implants. Reported success rates of 93.7% (one year) by Shernoff, 94.3% by Balshi and 100% (five years) by Smith and Kapur do not materially differ from those reported for the non-diabetic population. All studies to date however did not use proper controls, introduced several significant factors which were not controlled for in the design or analysis, lacked adequate well-defined success criteria or altered the patients' normal diabetic routine. No attempt was undertaken in any study to examine the peri-implant tissue behaviour over a prolonged period.

Animal studies using uncontrolled and controlled diabetic models have found less bone growth surrounding and less bone contact with various types of implants (Takeshita et al, 1997,

I propose to examine the impact of diabetes mellitus on the success/failure ratio of osseointegrated implants and its influence on the peri-implant bone behaviour of patients who have been treated in the Implant Prosthodontic Unit of the Faculty of Dentistry, University of Toronto, utilising a retrospective study approach. These outcome measures will be correlated with the type, the degree of control, the duration and the existence of complications of diabetes. The concurrent presence of other health problems and the use of smoking in the presence of diabetes will also be investigated.
Diabetes:

Epidemiology:

Diabetes mellitus is a widespread metabolic disorder characterised by hyperglycaemia due to a relative lack of insulin as a result of either defective insulin secretion, action or both (i.e. a relative or absolute shortage of insulin). 4-5% of the Canadian general population or approximately 1.5 million people (10.2 million in the US) has been diagnosed with one form of diabetes or another (Tan and MacLean, 1995). It is estimated that this number will reach 2.2 million by the year 2000 and 3 million by 2010 (Tan et al, 1997). Statistics obtained in the United States indicate that for every person diagnosed with diabetes there is another with undiagnosed disease. If the Canadian population follows the trend seen in the United States, it can be postulated that the prevalence of Diabetes is grossly understated and that the true prevalence is likely 8-10% of the population (Meltzer et al, 1998). The prevalence of diabetes increases with age from 2.0% at age 20-44 to 17.7% at age 65-74 and with a history of parental diabetes and obesity.

Diabetes is a serious health concern and accounts for 25% of end stage renal failures, 50% of lower extremity amputations, is the leading cause of blindness and accounts for 10% of all patient days in the hospital. It is the major cause of coronary artery disease; the number one killer in Canada. Diabetes can be a very debilitating disease and it can be said that patients with diabetes generally die younger than those individuals without diabetes for all age, sex and race groups (8 years shorter life expectancy for diabetic adults aged 55-64 and 4 years shorter for diabetic adults aged 65-74). In addition, the relative risk for all major causes of death except malignancy was elevated in diabetics. The rate of mortality is 57% higher for diabetic males compared to females and 27% higher for non-Hispanic black diabetics compared to non-
Hispanic whites. Death rates were highest for those individuals using insulin and for those having diabetes in excess of 15 years.

Large ethnic and geographic variation in prevalence exists. Inuit have the lowest reported prevalence of Diabetes while the Pima Indians and certain non-Caucasian inhabitants of the Pacific region have prevalences approaching 35%. Finland and Sweden have the highest incidence of Type 1 diabetes in the world for children under 15. Children from these countries, in fact have a risk 30 times higher than a similar child in Japan. In the U.S. the prevalence is 1.6 times higher in non-Hispanic blacks and 1.9 times higher in Mexican-Americans than in non-Hispanic whites. Rates appear to be the same for both sexes regardless of race.

The cost of diabetic management is enormous both to the individual and to the medical system. Based on figures from the USA, it has been estimated that one dollar out of every seven spent on health care is spent on the management of diabetes and its complications. Proper management has been shown to reduce the economic burden of this disease.

Due to the high prevalence, high morbidity and high costs associated with diabetes, diabetic care has been well studied and has become well organised in order to effect the most profound change in the disease's natural course. Diabetic health care teams headed by a primary health care provider and involving many disciplines including educators play an important role in addressing this significant health disorder.
Types of Diabetes:
There are many different types of diabetes based on an etiologic classification. There are four main classifications at this time: (Meltzer et al, 1998, Expert Committee on the Diagnosis and Classification of Diabetes)

Type 1 – diabetes primarily a result of Beta cell destruction, keto-acidosis present
Immune mediated or idiopathic

Type 2 – wide range, may be primarily insulin resistant to primarily insulin deficient

Gestational Diabetes – seen during pregnancy

Other specific types – generally uncommon, related to specific genetic defects, other diseases or drug use. (HNF = hepatocyte nuclear factor, DNA = deoxyribonucleic acid)

Genetic defects of beta-cell function
- Chromosome 12, HNF-1a
- Chromosome 7, glucokinase
- Chromosome 20, HNF-4a
- Nitochondrial DNA
- Others

Genetic defects in insulin action
- Type A insulin resistance
- Leprechaunism
- Rabson-Mendenhall syndrome
- Lipodystrophic diabetes
- Others

Diseases of the endocrine pancreas
- Pancreatitis
- Trauma pancreatectomy
- Neoplasia
- Cystic Fibrosis Hemochromatosis
- Fibrocalculous pancreatopathy
- Others

Endocrinopathies
- Acromegaly
- Cushing’s syndrome
- Glucagonoma
- Pheochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma
- Others

Infections
- Congenital rubella
- Cytomegalovirus
- Others

Uncommon Immune-mediated
- Stiff-man syndrome
- Anti-insulin receptor Antibodies
- Others

Drug or chemical induced
- Vacor
- Pentamidine
- Nicotinic Acid
- Glucocorticoids
- Thyroid hormones
- Diazoxide
- Beta-adrenergic agonists
- Thiazine
- Dilantin
- Alpha-interferon
- Others

Other genetic syndromes
- Down’s syndrome
- Klinefelter’s syndrome
- Turner’s syndrome
- Wolfram’s syndrome
- Friedreich’s ataxia
- Huntington’s chorea
- Laurence-Biedel syndrome
- Myotonic dystrophy
- Porphyria
- Prader-Willi syndrome
- Others
Gestational Diabetes:

Gestational diabetes (GDM) is a form of the disease, which develops during pregnancy, usually during the third trimester and occurs in 2-4% of all pregnancies or approximately 130,000 individuals per year in the U.S. However, the prevalence may be as high as 14% depending upon the population being studied. It is most common in women over 25, who are obese, who are of an ethnic group predisposed to diabetes (Aboriginals, Hispanics, Asians and Africans), and who have a history of diabetes or who have given birth to babies with a birth weight over 4 kg (Naylor et al, 1997, American Diabetes Assoc, 1998).

GDM has been defined as any degree of glucose intolerance with onset or first recognition in pregnancy. This definition applies whether diet or insulin is used to control it and whether it persists after pregnancy. The patient should be classified 6 weeks post-partum as:

1. Normoglycaemic
2. Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG)
3. Diabetic.

GDM is diagnosed based on oral glucose tolerance test (OGTT) blood glucose levels using cut-off points or levels established in a study by O’Sullivan and Mahan in 1964 (O’Sullivan and Mahan, 1964). GDM is diagnosed when the blood glucose levels in two or more out of 4 OGTTs are more than or equal to two standard deviations above the normal levels. This was altered in 1979 by converting the glucose values in whole blood to plasma values (Landy et al, 1996)

Recently, it has been suggested that these values may be too high and that patients are being missed. Carpenter and Coustan have recalculated the values and the WHO has suggested standardising the screening test to utilise a 75 gm load OGTT (Carpenter and Coustan, 1982,
WHO, 727). Both of these measures identify more individuals with maternal and perinatal complications associated with high plasma glucose levels.

GDM should be diagnosed by measuring the fasting plasma glucose (FPG) level and plasma glucose levels at 1 and 2 hr after ingesting a 75 gm-glucose load. If two of the three values are met or exceeded a diagnosis of GDM is established. If only one value is met then the diagnosis of impaired glucose tolerance should be made.

Fasting > 5.3 mmol/L
1 hour > 10.6 mmol/L
2 hour > 8.9 mmol/L  (Meltzer et al, 1998)

**Impaired Glucose Tolerance (IGT) AND Impaired Fasting Glucose (IFG):**

These terms refer to metabolic states intermediate to normal glucose homeostasis and diabetes.

IFG is defined as a glucose level > or = 110 mg/dl (6.1 mmol/l) but less than 140 mg/dl (7.8 mmol/l). The threshold level of 110 mg/dl was chosen somewhat arbitrarily but is the level above which the incidence of micro and macro vascular complications increases (Report of the Expert Committee on the Diagnosis and Classification of Diabetes, 1997).

IGT is seen in individuals who very often are euglycaemic in their daily lives and have normal or nearly normal glycated haemoglobin levels. It is only when challenged by glucose load such as is used in an OGGT that they become hyperglycaemic.

IFG and IGT are not clinical entities in their own right but rather are significant as risk factors for diabetes and cardiovascular disease (Edelstein et al, 1997). Both are associated with insulin resistance which is associated with Type 2 diabetes, low HDL levels, hypertension, hypertriglyceridaemia which is associated with small dense LDL and increased plasminogen activator inhibitor -1 (PAI-1) levels. Low HDL levels increase the risk of atherogenesis and
increased levels of PAI-1 inhibits fibrinolysis. Both of these contribute to a higher risk of cardiovascular disease (Ferrannini and Canastra, 1998, Goke, 1998).
ETIOLOGY:

Diabetics experience a wide range of signs and symptoms as a result of the hyperglycaemia resulting from the impaired action of insulin. Polyuria, polydipsia, weight loss, polyphagia and blurred vision are the most common symptoms reported. Susceptibility to infection and growth impairment may be seen if the hyperglycaemia is chronic. Acute life threatening consequences such as keto-acidosis and non-ketotic hyperosmolar syndrome may be the consequence of untreated or poorly managed diabetes.

Diabetes also carries with it a plethora of serious long-term complications. Such things as retinopathy leading to blindness, nephropathy resulting in renal failure, and micro and macro angiopathy leading to atherosclerotic heart disease, cerebrovascular disease and peripheral vascular disease. Peripheral neuropathy with its risk of foot ulcer, amputation and Charcot joints and autonomic neuropathy which causes gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction are very common complications of this widespread metabolic disorder. In addition, diabetics may also experience hypertension, abnormalities in lipoprotein metabolism and periodontal disease. Emotional and psychosocial disruption are also quite common (Meltzer et al, 1998).

Several pathogenic processes are at work in the pathogenesis of diabetes. The processes involved range from an autoimmune disorder which results in the destruction of the Beta-cells of the Islets of Langerhan in the pancreas resulting in an insulin deficiency to abnormalities which result in a resistance to insulin's action. As a result of the reduced action of insulin, abnormalities in carbohydrate, fat and protein metabolism are seen in target tissues. Both reduced secretion of insulin and insulin resistance are often seen in the same patient and as a result it is often unclear which is the primary cause of the hyperglycaemia. Glycation of tissue protein as well as other
macromolecules and the production of high levels of polyol compounds from glucose are thought to be part of the mechanism involved in the pathogenesis of the tissue damage.

The majority of diabetic cases can be divided into two broad groups, Type 1 and Type 2 diabetes. In general, Type 1 diabetics have an absolute deficiency of insulin secretion while Type 2 diabetics have both a resistance to insulin action as well as a reduced compensatory hypersecretion of insulin. Type 2 diabetes has by far the highest prevalence.

**TYPE 1 DIABETES:**

This type of diabetes is thought to be an autoimmune disorder (Thorsby et al, 1998), which results in either the slow or rapid destruction of the Beta-cells of the Islets of Langerhan of the pancreas. It commonly occurs in childhood but also may occur at any age even into the 8th and 9th decades of life.

In general, Type 1 diabetes is thought to develop as a result of a polygenic predisposition to autoimmune destruction (Thorsby et al, 1998). It has been demonstrated that the risk of Type 1 diabetes increases 11 fold if the father is a Type 1 diabetic and 20 times if the brother is (Wadsworth, 1997, Altobelli et al, 1998). However, it has also been shown through twin studies that genetics is not the entire story as diabetes is found in only 30-50% of identical twins despite them having identical genetics (Gorsuch et al, 1982, Johnston et al, 1983, Hawkes, 1997).

The disorder is strongly associated with the MHC HLA region of chromosome 6 (Cudworth and Wolf E, 1983) which appears to contribute approximately 35% to the genetic susceptibility and with the DQA and B alleles and it is also influenced by the DRB genes (Cudworth, 1978). These HLA-DR/DQ alleles can be either predisposing or protective. Positively charged amino acid residue (aspartate) are protective while non-charged residues at
position 57 of the DQ Beta chain of the DQ heterodimer are positively associated with Type 1 diabetes. Twelve other genetic foci mapping to various chromosomes have been identified as having an influence on the incidence of diabetes Type 1 (Hattersley, 1997). The variation in the incidence of diabetes among races can at least in part be explained by the variation in the incidence of high-risk genotypes (Sperling, 1997, Bosi and Sanugeri, 1998).

It appears that the susceptibility locus lies 5 sequences upstream from the insulin gene in an area which is highly polymorphic and which is composed of randomly repeated 14-15 base pair sequences. The number of repeats varies and can be generally divided into three distinct groups or classes; Class 1 (26-63), Class 2 (average 80, rare in whites) and Class 3 (141-209). Generally speaking Class 1 alleles are associated with Type 1 diabetes while Type 3 is seen to be protective. The exact mechanism by which the polymorphism is translated into auto-immunity is not as yet fully understood (Shield and Baum, 1998).

These alterations in the MHC (major histocompatibility complex) alleles may result in an alteration in the function of the MHC" produced. In general the MHC group of proteins is responsible to present to the immune system peptide epitopes of processed antigen. It is speculated that the modified MHCs present epitopes of auto-antigens such as peptides of the insulin molecule (Durinovic-Bello, 1998). This results in sensitisation of the T-cells of the immune system to the insulin molecule and precipitates an autoimmune attack on the islet cells by cellular elements. Humoral auto-immunity to insulin has been demonstrated predominantly in childhood while cellular auto-immunity to insulin has been shown to be relatively low in the peripheral blood. However, T-lymphocytes have been isolated within the Islets of the pancreas, which have a high reactivity to insulin in pre-diabetic individuals. It appears that insulin may act as an early auto-antigen and target the immune response specifically to the Beta-cells of the
Islets of the pancreas (Bosi and Sanugeri, 1998). It has been noted that auto-immunity to various auto-antigens occurs simultaneously with the diagnosis of diabetes. Cellular reactivity to insulin auto-antigen has been found to occur with similar frequency in both pre-diabetic and control individuals. It is postulated that in those individuals in the pre-diabetic state, the auto-immunity targets the destruction to the Beta-cells but that this immune sensitisation spreads with time to a variety of other auto-antigens in order for insulitis and clinical disease to develop (Mirakian et al, 1982). Due to similarities in auto antigens and environmental antigens, auto-immunity may spread and amplify by repeated exposure to these various environmental antigens (Durinovic-Bello, 1998).

Various environmental factors have been investigated (Akerblom and Knip, 1998) but the data is quite confused and no clear answer has been forthcoming. Cows’ milk has long been implicated in the development of Type 1 diabetes but still remains a controversial factor (Bosi and Sanugeri, 1998). The immune response to milk protein in Type 1 diabetic is very heterogeneous, the sequence homology with autoimmune antigens is questionable and the protective effect of breast milk appears to be minimal. All of these factors weaken the argument that cows’ milk may be an environmental factor in accelerating the autoimmune process against the Islet cells. It has recently been demonstrated that children fed cows’ milk developed antibodies to bovine insulin due to its presence in the cows’ milk and that cross reactivity to human insulin could be demonstrated as human insulin and bovine insulin vary by only three amino acids (Vaarala et al, 1998). It is speculated that it may be the bovine insulin reactivity in predisposed individuals, which precipitates the insulitis and Beta cell destruction (Murch, 1996, Cavallo et al, 1996).
Viruses have also been implicated in the acceleration of the autoimmune process. Seasonal variation in the incidence of diabetes has been confirmed but the isolation of viruses from the islet cells remains anecdotal. Interestingly, it has been shown recently that mothers of future diabetics often have an enteroviral infection during pregnancy (Lonnrot et al, 1998). Investigation is now underway to determine if endogenous retroviruses might act as an autoimmune gene or as an infectious agent.

In contrast to this, there is some evidence that infections in the first year of life may indeed offer protection to the individual from the onset of diabetes. This hygiene hypothesis states that fewer microbial infections early in life increases the individuals susceptibility to Type 1 diabetes and is based on the observation that communities with lower populations and smaller families have a higher incidence of Type 1 diabetes. Furthermore, it has been found using BB rats, a strain of rats which spontaneously develops Type 1 diabetes mellitus and non-obese diabetic (NOD) mice in germ free environments, that the incidence of Type 1 diabetes increased but was greatly reduced by either viral infection or exposure to bacterial antigens early in life. Gibbon et al found that infection during the first year of life was associated with a reduction of diabetes risk. He postulates that this may be due to modifying the lymphatic response to subsequent immunological challenge (Gibbon et al, 1997).

Four different types of antibodies related to the onset of Type 1 diabetes have been identified to date; islet cell antibodies (ICA), antibodies to the IA-2 protein (IA-2A), antibodies to the 65-kD isoform of glutamic acid decarboxylase (GADA) and insulin antibodies (IAA). These antibodies are the first detectable markers of the destruction taking place within the Islets of the pancreas and can in fact be used to predict those individuals likely to develop Type 1 diabetes. These antibodies attack the various proteins of the Beta-cells of the Islets (Lendrum et
al, 1976) and result in the calling and activation of macrophages (Arnush et al, 1998). These cells in turn produce various cytokines associated with insulitis and Beta-cell destruction. Cytokines (IL-1, TNF alpha, TNF Beta, and IFN gamma) are directly cytotoxic to the Beta-cells by inducing the production of nitric oxide and oxygen free radicals within the Beta cells. They may also increase the T-cell mediated cell destruction by up regulating the MHC class 1 expression on the Beta cells (IFN gamma) and inducing Fas expression on the Beta-cells (IL-1, TNF alpha and gamma) (Rabinovitch, 1998).

Jones et al examined the role of other environmental factors on the development of Type 1 diabetes and found that there was no association with such things as birth weight, gestational age, birth weight for gestational age, maternal age or parity. He did however find a slight increased risk with not breastfeeding and with the presence of gestational diabetes. In addition, the presence of pre-eclampsia or eclampsia significantly increased the risk of Type 1 diabetes. It is speculated that pre-eclampsia may be the result of an immunological incompatibility between the mother and foetus and as a result of this early immunological disturbance within the foetus, the incidence of Type 1 diabetes increases (Jones et al, 1998).

Despite the rather lengthy and somewhat complicated discussion above, it appears safe to state that Type 1 diabetes is an autoimmune disease resulting in the destruction of the Beta-cells of the Islets of Langerhan in the pancreas resulting in a loss of the ability to produce insulin. This disorder appears to have a genetic predisposition that varies in its expression. This variance in expression may be the result of an environmental factor or group of factors, which heightens the expression of the autoimmune process. These environmental factors remain to be positively identified but have been speculated to be dairy protein, and viral or bacterial infection. Recognition of the autoimmune nature of the process has led to identification of antibodies
which can now be utilised to predict with a reasonable degree of accuracy those individuals likely to develop Type 1 diabetes (Kulmala et al, 1998). It is speculated that by developing an understanding of the molecular and cellular mechanism involved in the development of Type 1 diabetes, preventive measures will be able to be undertaken early in the predisposed individual's life to prevent the onset of this metabolic disorder (Sperling, 1997, Schranz and Lenmark, 1998, Shield and Baum, 1998).

**TYPE 2 DIABETES:**

Type 2 diabetes (formerly known as growth onset or non-insulin dependent diabetes) is the most prevalent form of diabetes (Bloomgarden, 1998) and is the result of insulin resistance and a relative insulin deficiency but may range to a predominantly secretory disorder with insulin resistance (Meltzer et al, 1998, Goke, 1998). In fact many of the individuals afflicted with this condition will never need insulin replacement. It appears that many different factors are involved in the pathogenesis of this diabetes type (Sacks and McDonald, 1996) and generally this form can go undiagnosed for many years as the hyperglycaemia often develops slowly and in the early stages is often not severe enough to give rise to the classic symptoms of diabetes.

The risk of developing this form of diabetes increases with increasing weight (obesity) (Wang SL et al, 1997, Ferrannini and Camasta, 1998); increasing age and reduced activity (Boucher, 1998). As well the incidence is elevated in women with a history of gestational diabetes (GDM) (Buchanan et al, 1998) and in those individuals with a history of hypertension and dyslipidaemia (Gorden, 1997, Paolisso and Howard, 1998,). Certain races such as the Pima Indians (Pratley, 1998) and certain Native Canadian Indians appear to have a genetic predisposition (Harris et al, 1996).
Acute complications such as ketoacidosis are rare in this form of the disease, however long term complications such as micro and macro angiopathy, retinopathy, nephropathy and neuropathy are not uncommon and may already be present by the time the initial diagnosis is made. Patients with this disease often present with normal or even elevated insulin levels but having said this; given the levels of hyperglycaemia found, the insulin levels are still below what would be expected. This suggests not only insulin resistance but also a secretory disorder in the Beta cells.

The present theory of the development of Type 2 diabetes concerns itself with a two step model. The primary event in the development of diabetes is the development of insulin resistance, which in turn leads to the development of impaired glucose tolerance. Further insulin resistance and the imposition of Beta-cell dysfunction result in the development of diabetes. The best predictor of progression from impaired glucose tolerance (IGT) to Type 2 diabetes is an elevated 2hour-post load oral glucose tolerance test (OGTT) (Edelstein et al, 1997). As well, the presence of a fasting hyperinsulinaemia and a low glucose removal rate or a high fasting proinsulinaemia are predictors of the development of Type 2 diabetes. The former tests are suggestive of insulin resistance while the latter test is suggestive of Beta-cell dysfunction.

As stated earlier the various risk factors (Bloomgarden, 1998) involved in the development of Type 2 diabetes are:

1. Age
2. sex
3. family history of diabetes
4. obesity
5. sedentary life style
5. smoking
6. poly-cystic ovary disease
7. high levels of TNF-a
8. Vitamin D deficiency

Age: An increased incidence of Type 2 diabetes with ageing has been noted particularly in individual with a genetic predisposition. In these individuals, if they develop IGT early in life the likelihood of progression to Type 2 diabetes increases. The later in life that IGT develops, the less likely a progression to diabetes will occur.

Sex: The prevalence of Type 2 diabetes is higher in males than in females. However in women the combination of increased BMI (body mass index) and hyperinsulinaemia act synergistically to increase the risk of developing Type 2 diabetes beyond the simple additive risk effect seen with these to factors in males (Harris et al 1996).

Family History: A higher incidence and prevalence of Type 2 is found in the Pima Indians of Arizona, the Narua Indians and certain North American Indian tribes and genetic factors have recently been confirmed in these peoples. In addition, a higher incidence is seen in individuals of Hispanic and Mexican-American lineage. The genetics appear to be very complex and are likely polygenic in nature (Fujimoto, 1996). To date genes on chromosomes 1, 2 and 12 have been implicated in the pathogenesis of this disorder. It appears that the genetic defect may involve alterations in the precursors of hyperinsulinaemia and hyperglycaemia. Simple genetics however, does not totally explain the pathogenesis of Type 2 diabetes. The pathogenesis appears to be the complex combination of genetics and environmental risk factors that results in the development

**Smoking:** Several studies have shown that smoking contributes to insulin resistance and in so doing contributes to an increased risk of developing Type 2 diabetes. One study (Persson et al, 1997) found that the relative risk if Type 2 diabetes was 2.7 for men smoking 16 or more cigarettes per day. Targher found higher insulin and C-peptide response to oral glucose in cigarette smokers than in non-smokers with Type 2 diabetes (Targher et al, 1997). Glucose disposal was 42% lower in smokers than in non-smokers and a dose dependant increase in this percentage was noted based on the number of cigarettes per day. This suggests that smoking reduces insulin sensitivity in Type 2 diabetics (Kawakami et al, 1997).

**Poly-Cystic Ovary Syndrome (PCOS):** An increased incidence of Type 2 diabetes has been noted in patients suffering from PCOS (Sardesai et al, 1997). It is postulated that this is due in part to the hyperandrogenism present in these women as Foss et al found that treatment with the gonadotropin releasing hormone leuprolide decreased insulin levels (Foss et al, 1997). Batty et al found that the anovulatory women versus the ovulatory women with PCOS had higher fasting insulin levels and decreased insulin sensitivity (Batty et al, 1997). Providing antiandrogens (flutamide) to patients with PCOS resulted in lower insulin levels 120 min. after oral glucose suggesting a restoration of insulin sensitivity to some degree (Sanchez-Cervigon et al, 1997). This effect may be due an altered sex hormone carrying capability of serum albumin due to glycation of the protein (Hanna et al, 1997).

**Obesity:** An increased incidence of Type 2 diabetes is seen in those individuals who are obese Bloomgarden, 1996). It has been stated that as the body mass index (BMI) increases the incidence of diabetes increases independent of the fasting or 2 hr OGTT levels at baseline (Perry
et al 1995). It has been reported that it is not only the degree of obesity but the presence of changes in weight and the duration of the obesity that are factors having a linear relationship on the increased incidence of Type 2 diabetes. As the BMI increases insulin sensitivity decreases. This leads to increased production of insulin by the Beta-cells. This demand for increased production over a prolonged period of time results in defects in the Beta-cells (Ferrannini and Camasra 1998)

Various theories pertaining to the cause of the reduced insulin sensitivity associated with obesity have been put forth (Paolisso and Howard, 1998). Free fatty acids are elevated in the obese person (Boden, 1997). With the increase in the levels of free fatty acids the insulin stimulated uptake of glucose is inhibited in a dose dependant manner by:
1. inhibition of glucose transfer or phosphorylation
2. decrease in muscle glycogen synthase production
3. stimulation of hepatic glucose production
4. stimulation of the production of insulin in the non-diabetic to help compensate for the FFA inhibition of glucose uptake and insulin resistance.

In those individuals developing Type 2 diabetes FFA fail to stimulate the production of insulin. The individuals therefore develop hyperglycaemia due to the impaired glucose uptake and the increased hepatic glucose production. (Boden, 1997)

Leptin is a hormone produce by the adipose tissue and appears to play a role in obesity and possibly in the development of Type 2 diabetes (Bloomgarden, 1996, 1998). Leptin is found in both men and women although its levels are generally higher in women (Vauhkonen et al, 1997). Its level reduces with dieting or fasting and and during exercise and rises at night, during
feeding and during insulin infusion (Tuominen et al, 1996, Bloomgarden, 1996). Various studies have linked leptin with insulin resistance in skeletal muscle cells (Gabriel et al, 1996, Zimmet et al, 1996, Robbins et al, 1996). Others however, have reported similar leptin levels in obese individuals with or without diabetes Type 2 (Schwartz et al, 1996, Wei et al, 1996). It appears that there is a complex interaction of leptin resistance, obesity and insulin resistance and that leptin is a normal mediator of satiety.

In addition high levels of TNF-a has been shown to be associated with increased insulin resistance. This is believed to be due to decreased activation of the insulin receptor substrate and phosphatidylinositol 3 kinase, prevention of increases in membrane associated protein kinase C Beta and reduced amounts of adipocyte insulin induced 2-deoxyglucose uptake. Elevated levels of TNF-a have been identified in obese individuals (Kahn, 1995).

While obesity appears to be a risk factor in the development of Type 2 diabetes it is not only the BMI which is important but also the distribution of the adipose tissue in the body. A central visceral adiposity appears to present the greatest risk (Fujimoto et al, 1996, Wang et al, 1997).

**Low Birth Weight:** This factor is somewhat controversial as studies have been reported demonstrating both an increased risk of IGT and diabetes as well as no effect on these two entities. Carlsson et al, 1997 and Brand et al, 1997 each reported an association with low birth weight and an increased risk of developing IGT and diabetes due to insulin insensitivity while Shaw et al, 1997 reported an increased risk as a result of reduced Beta-cell function. On the other hand, Vanhala et al, 1997 found no such relationship. Valle et al, 1997 reported that low birth weight infants of diabetic mothers when compared to low birth weight infants of diabetic fathers had a stronger association with adult risk factors of diabetes. This suggests that the intra-uterine
environment may play a role in the development of diabetes. A thrift genotype appears to be expressed as a result of poor nutrition in the intra-uterine environment and poor early post-partum nutrition (Groop and Tuomi, 1997). This genotype is expressed in an effort to alter metabolic functions to favour brain over gut functions (Hales, 1997). Indeed, if one examines the offspring of diabetic mothers there is a U shaped curve representing the incidence and prevalence of diabetes. The one arm represents the low birth weight offspring while the other represents the typical overweight diabetes prone, offspring of diabetic mothers.

**Gestational Diabetes (GDM):** Buchanan in an interesting study on the effects of GDM on the development of postpartum diabetes and IGT reported that ante-partum hyperglycaemia and poor insulin responses to oral glucose were independent risk factors in the development of diabetes postpartum. In addition, he found that poor insulin response to intravenous glucose, an early gestational age at diagnosis of GDM and significant weight gain between pre-pregnancy and postpartum periods were predictors for postpartum IGT which has a very high association with development diabetes. Chronic insulin resistance and altered Beta-cell function appear to be at play in the development of either of these conditions (Buchanan et al, 1998).

Examination of the pathogenesis of Type 2 diabetes leads one to conclude that we most likely are dealing with a polygenic disorder whose expression is strongly influenced by multiple environmental factors.
SIGNS, SYMPTOMS AND DIAGNOSTIC CRITERIA:

The usual and customary signs and symptoms of untreated Diabetes Mellitus are:

1. Polyuria
2. Polyphagia
3. Polydipsia
4. Increased incidence of infection
5. Increased incidence of periodontal disease.
6. Pruritus
7. Weakness and fatigue
8. Headache
9. Weight loss or gain
10. Nausea and vomiting
11. Dehydration
12. Confusion
13. Acetone breathe


**Diagnostic Criteria:**

The following are the most recent recommendations of the Expert Committee on Diabetes for the diagnosis of diabetes:

**FPG.**, < 6.1mmol/ (100mg/dl) = normoglycaemic

**FPG.**, < or = 6.1mmol/L (110mg/dl) but < 7.0mmol/L (126mg/dl) = IFG

**FPG.**, > or = 7.0 mmol/L (126 mg/dl) = provisional diagnosis of diabetes to be confirmed on a subsequent day by

1. **FPG.**, > or = 7.0mmol/L (126mg/dl) or
2. **OGTT** with a 2 hr. post load plasma glucose > or = 11.1 mmol/L (200mg/dl) or
3. **Symptoms** with plasma glucose of > or = 11.1 mmol/L (200mg/dl).

The corresponding OGTT levels are as follows:

**2-h post load glucose (2hPG)< 7.8mmol/L (140md/dl) = normal tolerance**

2hPG > or = 7.8mmol/L (140mg/dl) and < 11.0 mmol/L (200mg/dl) = IGT

2hPG > or = 11.1mmol/L (200mg/dl) = provisional diagnosis of diabetes to be confirmed as noted above.
Management of Diabetes:

The goal of management of diabetes is to reduce the levels of blood glucose toward the normal range as this has been shown to reduce the incidence of both the micro and macro vascular complications (DCCT, 1993, Ohkubo et al, 1995, Turner et al, 1996). In addition, reduction of the free fatty acid levels aids in reducing the incidence of coronary artery disease (CAD) (Pyorala et al, 1997). Target levels to achieve these goals are still undergoing revision.

Proper management of the diabetic begins with a thorough history and physical examination to determine the overall state of health of the individual. The history should focus on signs and symptoms that are present and should attempt to identify any risk factors for chronic disease. The physical examination should pay close attention to those systems affected by the disease. Laboratory tests should include glycated haemoglobin levels and plasma glucose levels. These tests will provide information about the patient’s glycaemic control and the accuracy of their self-monitoring. Self-monitoring has been of great benefit to individuals with diabetes. It helps them recognise periods of hypoglycaemia and to assess the effects of diet, exercise, and therapy (Meltzer et al, 1998).

The expert Committee on Diabetes has established 4 glucose target levels for adults and adolescents with diabetes:

1. **Ideal levels** are levels within the normal range with people without diabetes. These are achievable early after diabetes onset in those managed with diet but rarely in those managed with pharmacological therapy (DCCT, 1993).

2. **Optimal levels** are those that approach normal and are associated with a low incidence of the serious complications of diabetes. These levels may be impossible to attain in some without
serious side effects such as hypoglycaemia, decreased quality of life and difficult to obtain in many despite intensive therapy (DCCT, 1993).

3. **Suboptimal levels** are attainable by most individuals with diabetes, and are in the 7.1 – 10.0 mmol/l range before a meal and in the 11.1 – 14 mmol/l after a meal (DCCT, 1993).

4. **Inadequate Glucose levels** are associated with both acute and chronic complications and require reassessment and readjustment of therapy.

Table 1

<table>
<thead>
<tr>
<th>Levels of Glucose Control for Adults and Adolescents with Diabetes Mellitus</th>
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<tbody>
<tr>
<td>Test</td>
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<tr>
<td>Glycated Hb (% of upper limit) HbA assay</td>
</tr>
<tr>
<td>Fasting or premeal glucose level (mmol/L)</td>
</tr>
<tr>
<td>Glucose level 1-2 hr. after meal (mmol/L)</td>
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**Metabolic Therapy:**

It has been determined that metabolic therapy should be instituted in a stepwise manner and should be dependant on the achievement of target levels of glycaemic control. It may involve diet control and modification as in Type 2 diabetes were weight loss and control of glucose and lipid intake are important (Brown et al, 1996) or it may be directed toward co-ordination of food intake and insulin dosages.

In addition to diet modification it has been demonstrated that increased physical activity promotes cardiovascular health, increased insulin sensitivity, lower blood pressure and an improved lipid profile (Pate et al, 1995). A gradual increase in physical activity may assist in glycaemic control and reduce the need for medication (Schneider et al, 1992, ADA, 1998). One
must be aware of the effects of exercise on glucose levels when undertaking an exercise program. It has been shown that moderate activity lowers blood glucose levels and may precipitate a hypoglycaemic episode while intense activity has an opposite effect and may in fact precipitate hyperglycaemia and ketosis. Furthermore one must be cognisant of the risks of exercise particularly in individuals which have macro or micro vascular complications. Macroangiopathy may result in an increased risk of cardiac ischemia or arrhythmia while microangiopathy may increase the risk of retinal haemorrhage and neuropathy may increase the risk of foot injury (Tsui and Zinman, 1997).

Drug therapy may involve oral hypoglycaemics such as the sulfonylureas, biguanide, alpha-glucosidase inhibitors and thiazolidinediones or insulin injections in its various formulas or both (Bloomgarden, 1998).

Sulfonylureas include drugs such as acetohexamide, chlorpropamide, glybide, glicazide, tobutamide, tolazamide. These drugs are primarily insulin secretogogues. They improve the insulin response to glucose stimulation and also improve glucose uptake. These drugs exert a powerful influence on the cardiac muscle and increase vascular resistance, decrease post-ischemic vasodilatation and reduce diazide-induced vasodilatation. They also are anti-arrhythmic and have been show to reduce CVD mortality. They work primarily by inhibiting the K sub ATP channels, which results in a depolarisation of the cell membrane. This increases the inflow of Ca 2+ that leads to a secretion of insulin (Groop, 1992, Zimerman, 1997).

Biguanides (metformin) work by reducing the hepatic glucose production, which reduces the hyperglycaemia. They may also enhance insulin mediated glucose uptake by the cells and may reduce absorption of glucose. They have an antiatherogenic effect as they increase fibrinolysis, decrease platelet aggregation, increase erythrocyte deformation, decrease lipid
incorporation into vessel walls, decrease vessel smooth muscle cell growth, and restore vasodilatation. In addition there is evidence that metformin aids in weight loss better than the sulfonylurias (Bell and Hadden, 1997).

Alpha Glucosidase inhibitors, such drugs Acarbose and Voglibase reduce glucose levels and glycosylated haemoglobin levels primarily by reducing the uptake of glucose and starches from the gut by increasing the production of GLP-1 (glucagon like peptide) which increases insulin secretion, inhibits gut emptying and helps regulate appetite (Balfour and Mc Tavish, 1993, Lebovitz, 1997).

Thiazolidinediones (troglitazone) increase insulin sensitivity and causes differentiation of adipocytes. Its exact method of action is uncertain at this time (Henry, 1997).

**Insulin therapy:**

Insulin therapy is necessary for the treatment of all Type 1 diabetics to prevent hyperglycaemia and life threatening ketoacidosis. It comes in several formulations and has been derived from both human and animal sources. Human sourced insulin is somewhat less anti-insulin antigen forming than is the animal derived formulas (Heding et al, 1984). Insulin is categorised based on its time of onset and duration. In ascending order these include lispro, regular, NPH, lente and ultralente insulin. These various insulins are often used in combination to effect the most successful control of glucose levels. The most frequent protocols are:

1. **Basal Bolus Protocol** - multiple daily injections of regular or lispro insulin before meals, NPH or ultralente as the basal type.

2. **Split-mixed Protocol** – mixture of regular and NPH administered before breakfast and dinner. Total of 2 injections per day.
3. **Type 2 diabetic routine**- a single injection of NPH insulin at bedtime with oral hypoglycaemics during the day.

4. **Subcutaneous insulin pump** – alternative to multiple daily injections

(DCCT 1995, Meltzer et al 1998)
COMPLICATIONS OF DIABETES:

Complications of diabetes can be divided into acute and chronic complications. The acute complications are hypoglycaemia and hyperglycaemia with ketoacidosis and hyperglycaemic-hyperosmolar states.

Long term complications may occur in both Type 1 and Type 2 diabetes. These are macrovascular complications such as coronary artery disease, cerebrovascular disease and peripheral vascular disease; microvascular complications such as retinopathy, nephropathy, neuropathy and foot problems.

Acute Complications:

1. **Hypoglycaemia** is usually the result of a failure to take food, an overdose of insulin or hypoglycaemic medication or the consumption of alcohol. It presents with a rapid onset and resembles a fainting spell. It is characterised by the release of adrenaline, anxiety, irritability, confusion and disorientation. The pulse is generally strong and bounding, the skin is sweaty, the pupils are dilated and the patient may experience tingling in the periphery. This condition is treated by providing the patient with a rapid source of glucose such as orange juice.

2. **Hyperglycaemia** is caused by a relative or absolute deficiency of insulin. It is characterised by a slow onset with increasing drowsiness. The patient will present with dry skin, a weak pulse, hypotension, acidosis (deep breathing), vomiting, ketonuria, and ketosis which results in acetone breath and tachycardia. Providing insulin as well as intravenous infusion to correct the acidosis, dehydration and the other electrolyte imbalances treats this condition.
Chronic Complications:

Retinopathy:

Retinopathy is the major cause of blindness in North America and causes 86% of blindness in people with Type 1 diabetes and 33% of blindness in Type 2 diabetes (Klein and Klein, 1984). There are two types of retinopathy seen in diabetes, proliferative retinopathy and macular oedema. Proliferative retinopathy occurs in 2% of Type 1 diabetics, 14% of Type 2 diabetics who use insulin and in 3% of Type 2 diabetics not using insulin (Klein and Klein, 1992). Macular edema occurs in 11%, 15% and 4% of these groups (Klein et al, 1984). Diabetics also have an increased risk of cataracts (Klein et al, 1995).

Both of these conditions are rare in children under the age of 10 but the prevalence increases sharply after the individual has been diabetic with Type 1 for more than five years in the post-pubertal period. Retinopathy on the other hand is present in 21% of Type 2 diabetics at diagnosis (Klein et al, 1984).

Predictors for the progression of the retinopathy are:

1. length of diabetic state
2. higher glycated haemoglobin levels
3. more severe retinopathy
4. higher blood pressure- elevated diastolic increases macular oedema, elevated systolic pressure increase blindness
5. higher lipid levels- elevated cholesterol, LDL or triglycerides increases the amount of retinal hard exudate which increase the loss of vision
6. pregnancy in Type 1 diabetics (Meltzer et al, 1998)
Progress of retinopathy can be slowed by intense insulin therapy in Type 1 diabetics to achieve improved control (DCCT, 1993). This however has not been shown to be the case in Type 2 diabetics (Klein et al, 1994). These conditions are treated by laser surgery, focal for macular oedema and scatter for proliferative retinopathy (Ferris, 1993). Vitrectomy is also utilised in treatment (Diabetic Retinopathy Vitrectomy Study Research Group, 1988).

Nephropathy:

Nephropathy is the number one cause of end stage renal failure in Canada and the western world and is the result of micro-vascular disease of the kidney (Canadian Organ Replacement Registry, 1996). It leads to the need for renal dialysis, and for renal transplantation, results in elevated blood pressure and in high morbidity and mortality from cardiovascular complications (Wang et al, 1996). Microalbuminuria is the earliest reliable indication that progressive nephropathy has developed in the Type 1 and Type 2 diabetic (Mathiesen et al, 1995). Therapy is directed at intensive glucose control, reduction of the blood pressure, inhibition of the angiotensin-converting enzyme (ACE) and elimination of all cardiovascular risk factors (American Diabetes Assoc., 1994, 1996).

Neuropathy:

Neuropathy generally develops within ten years of the onset of diabetes in 40-50% of individuals with Type 1 and type 2 diabetes. 50% of these individuals are symptomatic with neuropathic pain. Individuals diagnosed with Type 2 diabetes often have some degree of neuropathy at diagnosis. Neuropathy on the other hand is generally not seen in Type 1 diabetics for at least five years (Partanen et al, 1995). This condition can affect both the somatic and the
autonomic nervous system and can affect both motor and sensory functions. Symptoms vary widely depending on which system and to what degree that system is affected. The patient may present with weakness (motor), loss of sensation or elevated sensation (sensory) or sexual dysfunction, GI symptoms, bladder problems or light-headedness (autonomic).

Intensive diabetic management has been shown to be helpful in reducing the incidence of neuropathy in both Type 1 and 2 diabetics (DCCT, 1993, Ohkubo et al, 1995). The use of tricyclic antidepressants, carbamazapine or mexiletine for the treatment of neuropathic pain is often effective. Non addictive analgesics may also be used (Max et al, 1987).

**Foot Care:**

Foot problems are the major cause of morbidity and mortality in diabetics (American Diabetic Assoc., 1997). They are caused by either neuropathy or peripheral vascular disease and are often caused by minor trauma that leads to skin ulceration, infection, gangrene and amputation. Diabetic foot ulceration is a major cause of hospitalisation and accounts for 20% of all admissions to hospital in the US. One third to one half of all lower extremity amputations in the U.S. occur in diabetics (50,000 amputations) at a cost of 500 million dollars per year.

Diabetics are eleven times more likely to experience an amputation than non-diabetics are. Their risk increases with previous ulceration, peripheral vascular disease (PVD), increasing age, neuropathy, structural deformities, renal transplantation, poverty and smoking (Bild et al, 1989). Prevention of amputation requires regular examinations for early detection, aggressive treatment of ulceration and vascular surgery if necessary. Proper footwear, smoking cessation and avoidance of foot trauma are essential (Malone et al, 1989).
Cardiovascular Disease and Hypertension:

Cardiovascular disease is a major cause of morbidity and mortality in both Type 1 and type 2 diabetics. Mortality rates are 2-4 times higher among diabetics than age and sex-match non-diabetics, and diabetic men are 2 times more likely to develop coronary artery disease or strokes than non-diabetic men (Fuller et al, 1983). Women are 3-4 times more likely to develop these problems. The outcome from infarcts is worse in diabetics and diabetics are more likely to develop congestive heart failure, are four time more likely to re-infarct, are 2 times more likely to develop arrhythmias and have a higher short and long term mortality rate than non-diabetics (Abbot et al, 1988). In addition to the CAD and the increased risk of stroke diabetics also have an increased risk of peripheral vascular disease (PVD) which contributes to a higher incidence of gangrene and limb amputation.

Hypertension is more common in the diabetic and complicates the CAD, PVD and cerebrovascular disease (Kannel and McGee, 1979). It frequently develops with the onset of nephropathy and is characterised by a rise in both the systolic and diastolic pressures. 50% of Type 1 diabetics of 30 years duration are hypertensive. In Type 2 diabetics the hypertension is very often related to the degree of obesity, to decreased physical activity and to older age and is often present at diagnosis of the diabetes (Dawson et al, 1993).

Cardiovascular complications of diabetes should be treated early and aggressively using anti-hypertensives, diuretics, Beta-blockers and ACE inhibitors. Elimination of risk factors such, as smoking and high cholesterol diets may be useful (Dawson et al, 1993). Increased physical activity may also lower the risk of CAD. Low dose acetylsalicylic therapy should be considered as a primary preventive therapy (Antiplatelets Trialists Collaboration, 1994).
Diabetes and Dentistry:

From the previous discussion of diabetes and its long and short-term implications on the body's functions, it is not difficult to imagine that it would have an impact on the oral cavity. This impact can be divided into four specific areas:

1. Oral manifestations
2. Periodontal Disease
3. Oral Surgery

Oral Manifestations:

Dental development may be altered by the presence of diabetes. Up to age 10.5 and up to 2.5 years after diagnosis, development of the individual appears to be accelerated (Bohatka et al, 1973), after which there appears to be a gradual retardation of development. This is postulated to be due to the effect of diabetes on the pituitary gland. Initially the pituitary is stimulated but as the duration of the disease increases, the gland becomes exhausted and development retards (Adler et al, 1973).

Prior to the discovery of insulin, diabetics suffered from an increased incidence of dental caries. This was due to increased secretion of glucose in the saliva and to decreased salivary flow (Lederer, 1909, Zilz, 1915). With the advent of insulin therapy, most studies have failed to demonstrate such an effect (Bernick et al, 1975, Faulconbridge et al, 1981). Wegener (1971, 1975) noted that immediately after onset of diabetes, the caries rate increased but subsequently returned to normal. Other investigators have found a lower than normal caries rate due to the reduced carbohydrate diet.
In addition, changes to saliva gland form and function has been reported. Several authors have reported salivary gland enlargement with uncontrolled diabetes. This enlargement reduces with control but apparently never returns to normal (Russotto, 1981, Rao and Rao, 1979). The enlargement is due to a non-neoplastic, non-inflammatory fatty infiltration with a reduction in the number of acini. Acinar hypertrophy, glycogenic degradation of the epithelial cells and microangiopathy are seen (Davidson et al, 1969, Rao and Rao, 1979).

Xerostomia has also been found in diabetics (Connor et al, 1970). Parotid salivary flow has been reported to be 1/3 of the normal flow. Thorstensson reported that both long and short duration Type 1 diabetics had significantly lower salivary flow rates than non-diabetics did and had higher levels of salivary glucose than normal controls. The pH, the buffering capacity, the number of colony forming units of Candida Albicans, lactobacilli and streptococcus mutans were found to be the same. Research has found that insulin enhances the action of UDPG pyrophosphorylase, an enzyme important in the metabolism of glucose to hexosamines and sialic acid that are components of salivary muco-protiens. It is postulated that the absence of insulin in Type 1 diabetes may lead to acinar hypertrophy due to an accumulation of substrate within the acinar cells (Sadurska and Szymczyk, 1978).

Various other non-specific findings have also been reported. Such things as glossitis, altered filiform papilla, altered taste, burning sensations in the mucosa and tongue, oral lichenoid reactions to chlorpropamide and increased incidence of oral candidiasis have been reported (Scully, 1998). Burning mouth and altered taste sensation may be the result of the xerostomia or as a consequence of diabetic neuropathy.

Lastly but perhaps most importantly diabetes has an impact on the periodontal health of the diabetic.
Periodontal Disease:

Numerous studies have been conducted over the years to examine the impact of diabetes on periodontal health (Salvi et al, 1997). Much of the early work involved patients with either no control or very poorly controlled diabetes and as a result significant oral manifestations were often reported (Kaplan, 1938, Rudy and Cohen, 1942). The relevance of these early reports to the findings in today’s diabetic population must be questioned because as a rule the level of control attained by today’s diabetics while not ideal is certainly better than that attained previously (Finestone and Boorujy, 1967, Glavind et al, 1968).

Uncontrolled diabetics frequently present with a combination of inflammatory and degenerative changes in their periodontal tissues ranging from gingivitis to severe periodontitis with purulence and lateral abscesses. Bone loss has been reported to increase as the severity of the diabetes increases (Turvonen and Knuuttila, 1982, Galea et al, 1986). Although the periodontal disease may be more severe in uncontrolled diabetics the lesion appears to be the same as is seen in the non-diabetic. Similarly no study has been able to produce periodontal disease without the presence of the typical microbes found to be the periopathogens in euglycaemic patients (Grant-Theule, 1996, Lehrer et al, 1981, Sznayder, 1978, Murrah, 1985).

Studies that have examined the periodontal tissues of controlled diabetics have found that a difference in the prevalence of periodontal disease still exists (Tervonen and Knuuttila, 1986). Bone loss and attachment loss is greater in diabetics and is greater still in those diabetics having the disease longer or those reporting more diabetic complications such as retinopathy (Hugoson et al, 1989, Glavind et al, 1968). Cohen et al, 1970 and Cenicola et al, 1982 found that diabetics had higher gingivitis and periodontitis scores in longitudinal studies despite the fact that the diabetics had the same or lower plaque scores when compared to normal patients. Thorstensson,
1995 found that 23% of long-term diabetics and 18% of short-term diabetics had severe periodontitis. In a second study she found 28.5 to 58.4% of long term Type 1 diabetics had severe periodontitis. When one contrasts these findings to those of Hugoson et al, 1989 who reported that severe periodontitis was evident in only 13% of the normal population; one cannot escape the conclusion that the prevalence of severe periodontal disease is indeed higher in diabetics. In addition, Thorstensson found that advanced periodontal disease appeared earlier in long-term diabetics when compared to short-term diabetics and non-diabetic controls.

Many studies have attempted to examine the patho-physiology of periodontal disease in the diabetic. Much effort has been expended looking at the microvasculature of the gingiva and the other periodontal tissues (Lin et al, 1975). Numerous reports have found microangiopathy of the periodontal vessels. This microangiopathy consisted of thickening of the basement membranes of the vessels and thickening and proliferation of the endothelial cells (Listgarten et al, 1974). It has been postulated that these vascular changes result in impaired biological function and that they act as a barrier to O2 diffusion, waste removal, leukocyte migration and movement of immunoglobulins (Listgarten, 1974). However these reports have failed to correlate these findings to an increased level of periodontal disease or gingivitis.

Crevicular fluid studies have found increased glucose levels in the fluid of diabetic children, an increased flow rate and a reduction in the level of cyclic adenosine monophosphate (cAMP). The significance of these findings is unclear.

Microbiological studies have been contradictory. Several have reported identical microbiota in the plaque of diabetics when compared to the euglycaemic patient (Zambon et al, 1988) while others have reported various alterations in the plaque of diabetics (Masimo et al, 1983). Thorstensson (1995) in well controlled study found that all identifiable periodontal
Pathogens were found in both diabetics and non-diabetics. However, *P. gingivalis* was found more often in long term diabetics and *A. Actinomycetemcomitans* (AA) was the only bacteria associated with deep periodontal pockets in diabetics while several other organisms were associated with these pockets in non diabetics. Serological studies showed elevated serum antibody titres to AA, *P. intermedia*, *C. sputigera* and *F. nucleatum*. Older diabetics also had higher titres of *P. gingivalis* and *F. nucleatum* than non-diabetics did.

Other investigators have focused their attention on collagen metabolism (Yue, 1986). Reduced collagen synthesis and increased collagenase activity have been found in diabetics (Ramamurthy and Golub, 1983). This combination results in impaired healing and an accelerated destruction of the periodontal tissues as a result of a periodontal pathogen attack (Fahey et al, 1991). Furthermore diabetics are known to have less well-mineralised bones as a result of nephropathy and secondary hyperparathyroidism. Additionally, some diabetics demonstrate altered PMN chemotaxis and phagocytosis and as a result have reduced or impaired host resistance to infection (Claggett, 1981, Manouchehr-Pour et al, 1981, Nicolo et al, 1989, Anil et al, 1990 a, b, c, Cutler et al, 1991.).

It appears that a complex interaction between diabetic control and the presence of periodontal disease exists. Not only does diabetic control impact on the incidence, prevalence and severity of periodontal disease but conversely the severity and control of periodontal disease impacts on the diabetic state. Out of control periodontal disease increases insulin resistance and interferes with metabolic control. It has been shown that control of the periodontal disease will assist in regulation of the diabetes.
Diabetes and Oral Surgery:

The management of the diabetic patient who is to undergo surgery is dependent on several factors:

1. Type and severity of the diabetes and the complications which exist
2. Type of anaesthetic
3. Extent of the surgery
4. Extent of interference with feeding postoperatively.

Uncontrolled or poorly controlled diabetics should not receive elective care until the disease is controlled. Patients with well controlled Type 1 and Type 2 diabetes can be treated as non-diabetics for routine needs. Procedures should be short, atraumatic and as stress free as possible. Appointments should be scheduled in the morning and patients should be directed to have a good breakfast and to take their medications as normal. If surgery is potentially stressful or extensive special dietary and medication alterations may be required. Hospitalisation may be required for very traumatic procedures or for brittle diabetics. Dental care and precautions should be appropriate to the patient's medical status and degree of diabetic complications present (Scully, 1998, Alexander, 1999).

It has been reported that diabetics have altered wound-healing capabilities and as such the healing of tooth sockets and periodontal surgical sites is often delayed. This has generally been reported in studies of uncontrolled diabetics and from animal studies which simulate uncontrolled diabetes (Devlin et al, 1996, Loder, 1988).

Animal studies using streptozotocin to induce an uncontrolled diabetic state have found inhibition of the healing of extraction sockets. This has been reported to be the result of altered
collagen metabolism in both the gingiva and the bone (Kurita et al, 1985, Hsieh et al, 1994. The effect appears to impact on all stages of collagen formation including synthesis, maturation and degradation. Such effects will of course alter the structural framework necessary for normal healing of wounds (Devlin et al, 1996).
Wound Healing:

Wound healing is a complex continuous process, which for review purposes can be divided into three phases:

1. Hemostasis and Inflammation
2. Proliferation
3. Maturation and Remodelling.

Failure or delay in any one phase will result in delayed or failed healing (Witte and Barbul, 1997).

Hemostasis and Inflammation:

Hemostasis precedes inflammation in the chain of events leading to wound healing. Wounding results in damage to blood vessels, which results in the extravasation of blood products, cells and platelets. Contact of the platelets with the collagen of the tissue results in the initiation of both the extrinsic and intrinsic coagulation cascades (Steed, 1992). The intrinsic system is activated by the Hageman factor contacting tissue collagen while the extrinsic system is activated by thromboplastin formed from phospholipid and glycoprotein which are released when blood contacts injured tissue. The result of both systems is the production of fibrin and fibrin polymerisation (Steed, 1997).

The presence of fibrin, fibronectin and their fragments results in the release of cytokines and growth factors from platelets. Such factors as platelet derived growth factor (PDGF),
transforming growth factor B (TGF-B), fibronectin, platelet-activating factor (PAF) and serotonin are released (Wahl and Wahl, 1992).

The fibrin clot allows cells such as neutrophils, macrophages, fibroblasts and endothelial cells to invade the damaged area (Kurkinen et al, 1980).

Inflammation follows haemostasis and is characterised by increased permeability of vessels mediated by histamine and chemotaxis of cells, release of cytokines and growth factors and activation of migrating cells (Barbul and Regan, 1997). With the increase in permeability of the blood vessels and development of a concentration gradient of chemo-attractive substances such as complement factor 4 (C4), inter-leukin-1 (IL-1), prostaglandin, tumour necrosis factor -a (TNF-a), transforming growth factor B (TGF-B), platelet factor 4 and bacterial products within the wound, the migration of cells into the fibrin clot begins (Steed, 1997). The first cells seen to migrate are the neutrophils. Neutrophils begin this process by margination within the lumen of the blood vessels. This process is regulated by receptors on the endothelial cells called selectins and by receptors on the neutrophils known as integrins. Chemotaxis is governed to some extent by surface cell receptors specific to certain chemotactic agents. This control allows only selected cells with these receptors to migrate into the site. For example PDGF is a very strong chemo-attractant for fibroblasts and smooth muscle cells but not for epithelial or endothelial cells (Witt and Barbul, 1997, Steed, 1997).

Chemotaxis is followed by activation of the attracted cells. This process results in the cells altering their metabolic makeup and results in the formation of new surface antigens, new cytokines and increased cytoplasmic toxicity. All cells participating in wound healing are activated although their role in wound healing may vary. For example, neutrophil activation is not critical to healing whereas activation of macrophages and lymphocytes is (Steed, 1997).
Macrophages are critical to proper wound healing (Leibovich and Ross, 1975). Their activation initially by platelet released factors and later by phagocytosis of collagen and later by release of lymphokines such as interferons (IFN) and interleukins by lymphocytes begins the process of wound debridement, matrix synthesis and angiogenesis. Their activation results in the synthesis of cytokines PDGF, TGF, IL, and TNF which mediate angiogenesis and fibroplasia (Polverini et al, 1977, Regan et al, 1991). Nitric oxide is also produced by the macrophage. This compound is important as an antimicrobial agent but also has been shown to play a key role in wound healing (Schaffer et al, 1997, Barbul and Regan, 1997).

Macrophages also assist in the activation of lymphocytes by the release of various cytokines. The lymphocytes in turn release interferons (IFN) and interleukins (IL) (Wahl and Wahl, 1974). These factors then feed back and activate macrophages and monocytes to produce TNF-a and IL-1. This feed back mechanism or paracrine mechanism ensures adequate supply of these cytokines in the wound during healing (Barbul and Regan, 1997).

Other cells such as the fibroblast and epidermal cells also undergo phenotypic changes. Fibroblasts from wounds demonstrate increased collagen synthesis and contraction but decreased proliferation compared to normal dermal fibroblasts (Regan et al, 1991). Phenotypic changes in fibroblasts is strongly influenced by macrophage derived cytokines as well as by the matrix surrounding them (Ehrlich and Krummel, 1996). Cell adhesion to the matrix promoted by fibronectin also alters the phenotype.

Alteration of the inflammatory response profoundly affects the cell activation and healing process. Diabetes results in a reduced inflammatory response with a concomitant reduction in the number of cytokines and a reduced chemotaxis of cells. This results in more infection and reduced collagen deposition (Fahey et al, 1991).
Proliferation:

This stage is characterised by the proliferation of fibroblasts and endothelial cells in response to cytokines and growth factors produced by macrophages, platelets and the cells themselves. Fibroblasts are derived from the surrounding tissue and endothelial cells are derived from intact venules close to the wound. These cells migrate into the fibrin network and begin to proliferate (Witte and Barbul, 1997). Endothelial cells form new capillaries by a process known as angiogenesis which is mediated by:

1. cytokines produced by platelets, macrophages and lymphocytes (bFGF, aFGF, TGFα, IL-1, EGF, GCSF, TGF-B) (Harlan, 1987)
2. low oxygenation (Remensnyder and Majno, 1969)
3. lactic acid (Imre, 1964)
4. extracellular matrix protein – lumenin, fibrinogen (Barbul et al, 1990)
5. biogenic amines. (Zauberman et al, 1969)

Angiogenesis is critical to wound healing in that it provides a new supply of growth factors. It ensures that the wound receives an adequate supply of blood. The control or limiting factor may be the oxygen tension within the tissue (Steed, 1997).

Many of the same cytokines that induce chemotaxis also induce proliferation. Epithelial cells proliferate at wound edges or within islands of undisturbed cells within the wound. Their stimulation is not yet fully understood but macrophages and the cells themselves appear to play a role in their activation. Mediators for the process appear to be:

1. loss of contact inhibition
2. contact with fibronectin

3. cytokines – EGF, TGF-b, bFGF, PDGF, IGF-1

(Barbul and Regan, 1997)

Control of this proliferative phase is not fully understood in terms of those factors that arrest the process although a negative feedback loop is suspected. Some cells such as neutrophils undergo apoptosis and are phagocytosed by macrophages. Macrophages may also meet the same fate or are picked up in the lymph system (Albina et al, 1990, Belligan et al, 1996).

**Maturation and Remodelling:**

During this phase that determines the ultimate strength of the healed wound, collagen is deposited into the wound matrix. The rate of formation, the quality of and the quantity of collagen deposited are determinants of the final strength of the healed wound. Diabetics often present with diminished collagen levels in wounds due to altered inflammation.

Initially the wound matrix consists of fibrin and fibronectin and thrombospondin (Kurkinen et al, 1980). These proteins assist in chemotaxis. Glycoaminoglycans, proteoglycans and others are secreted next and support further matrix deposition and remodelling (Witte and Barbul, 1997). Lastly various collagens are produced. Early on collagen Type III is produced, followed by Type I and Type II. The early wound matrix consists of 30% Type III collagen whereas the final mature scar contains only 10% Type III and 80-90% Type I collagen. The role of Type III collagen is not clear at this time (Clore et al, 1979). Collagen synthesis is elevated for four to five weeks following injury. This increased rate of synthesis is the result of both an increased number of producing cells and an increased rate of production by those cells (Barnes et al, 1975, Diegelmann et al, 1975).
The matrix structure also changes with time as the scar matures. Initially the fibrils are thin and arranged parallel to the skin. As time passes these fibres thicken and align themselves along the stress lines of the wound. This thickening and re-alignment of the fibres results in an increased tensile strength of the scar, however the strength of the tissue never reaches the strength of the intact skin (Doillon et al, 1985). Breaking strength increases from 3% of the intact skin at one week to 20% after three weeks to 80% of the intact skin after three months (Ehrlich, 1988). Thereafter there is no increase in strength.

Collagen from wound tissue is biochemically different than normal skin collagen in that it has greater hydroxylation and glycosylation. Glycosylation correlates with thinner fibre characteristics and may be a reason that diabetics have poorer healing responses. Collagen is synthesised intracellularly like any other protein and is characterised by repeating amino acid sequences, Gly X-Y where X is often proline and Y is often hydroxyproline. The collagen molecule undergoes eight post translation steps that ultimately lead to the triple helix protein, which is secreted, into the matrix as pro-collagen (Prokop and Kivirikko, 1995). Once secreted the C and N terminals of the procollagen are cleaved by procollagen C/N proteinases. The resultant protein is collagen, which is less soluble than the procollagen. As this process continues fibril formation occurs by the cross-linking of these molecules (Forrest, 1983).

At the same time that collagen is being formed it is also being metabolised by enzymes known as collagenases whose activity is linked to the cytokines. A delicate balance between synthesis and degradation exists with matrix accumulation being the result of the process favouring deposition. The balance appears to be regulated both by the cells themselves and the matrix. (e.g. breakdown products of fibronectin activate collagensases) (Juliano and Haskill, 1993). The cell matrix interactions, migration, adhesion, and synthesis are controlled by integrins.
These integrins change during healing with the early integrins favouring migration while the latter favour attachment and synthesis (Clark, 1993). Their expression appears to be controlled by the cytokines (Witte and Barbul, 1997, Steed, 1997).

As the wound continues to heal a process of wound contraction occurs whereby the scar itself is shortened. The mechanism of this process is not fully understood but two main theories exist:

1. **Specialised fibroblasts** known as myofibroblasts exist and contain actin filaments in their cytoskeleton. This actin permits contraction of the cell, which in turn contracts the wound (Darby et al, 1990).

2. **Fibroblast movement** across the collagen matrix allows for wound contraction (Ehrlich, 1988).

If one examines the wound fluid many different proteins and fragments of proteins are found. Among them is a group of protein known as cytokines. Their existence and concentrations vary during the various wound-healing stages and indeed the different concentrations or their presence at different stages may induce completely opposite processes. They may stimulate cell proliferation, chemotaxis, haptotaxis, angiogenesis, protein expression and enzyme production. They are named for the cell that produces them-PDGF, their biological action—TGF, or the cell on which they act—EGF. They can also act on adjacent cells (paracrine), on the cell producing the growth factor (autocrine) or within the cell producing the factor (entercrine). Some growth factors are transported attached to large carrier proteins and are called endocrine factors.

They are produced by a variety of cells and their effects are profound and widespread. (Steed, 1997)
All of these factors have been studied in vitro to elucidate their role in wound healing however not all have undergone clinical trials. Clinical trials with TGF-b, FGF, IGF have not yet been reported. Studies with PDGF have demonstrated some benefits of using this factor with decubitus ulcers and diabetic neuropathic foot ulcers. Studies with EGF have reported limited improvements in healing. In addition to these studies, clinical trials with platelet releasates (i.e. a solution containing PDGF, TGF-b, FGF, platelet factor 4, B-thromboglobulin, and PD angiogenesis factor) have been undertaken. This assures that the proportion of the growth factors and the growth factors themselves are the same as those found in healing wounds. The results of these studies involving wounds resulting from diabetic neuropathy, peripheral vascular disease, venous stasis and vasculitis have generally indicated a positive effect of this releasate on wound healing. One study however did report that platelet releasates resulted in an increased size of the wound. The clinical significance of platelet releasates remains undetermined (Steed, 1997).

**Bone Healing:**

Bone is a highly organised tissue composed of organic and inorganic components. The inorganic component is consists of hydroxyappetite and other calcium salts while the organic matrix is very similar to the dermal matrix and consists largely of Type I collagen, glycoprotein and proteoglycans.

Wounding of bone by either trauma or surgery results in disruption of the blood supply to the bone, which results in the death of the osteocytes. The death of these cells releases lysozymal enzymes that begin the process of dissolution of the organic and inorganic matrices. Blood vessel disruption also results in the commencement of the hemostatic and inflammatory processes seen in dermal tissue (Urist, 1965). Osteoprogenitor cells migrate to the site and begin to differentiate
into osteoblasts while macrophages and giant cells debride the wound. Osteoclasts begin the process of osteolysis. Fibroblasts, osteoblasts, and chondroblasts differentiate from the progenitor cells derived from the periosteum and the marrow. With rapid stabilisation and fixation, fracture site and surgical wound healing proceeds by primary bone healing. Osteoprogenitor cells invade the organised clot, differentiate into osteoblasts and clasts and begin the process of new bone formation (Mast, 1997). A number of soluble growth factors modulate and mediate this process. Osteogenins are obtained from demineralized bone. The most widely studied of these is BMP (bone morphogenic protein) which belongs to the TGF-β supergene family. BMP stimulates undifferentiated cells in the periosteum to differentiate to chondroblasts and osteoblasts (Szachowicz, 1995, Dixon et al, 1996). It has been shown to stimulate ectopic bone formation, to enhance bone production and to stimulate bone repair in experimental non-union (Takagi and Urist, 1982, Toriumi et al, 1991). Other factors involved in the bone healing process are PDGF, TGF-B, FGF, and pro-inflammatory cytokines such as TNF-a (Ham, 1997). As well osteoclast growth factor stimulates osteoclastic bone resorption. Once healed, reorganised and matured, the new bone is indistinguishable from the surrounding old bone.

Out of early investigation into microcirculation and wound healing came the concept of integrating a metal root analogue into the jawbones, to be used to assist in the retention of missing teeth and support structures.
Dental Implantology:

History:

Implants are not a new therapeutic phenomenon since history records that man has, over time, attempted to find methods of replacing the missing parts of his oral apparatus. Evidence dating back to 600 A.D. in the Myan era, has demonstrated that shell teeth were implanted into the jaw to replace missing teeth. Throughout the years various materials such as shell, gold, iridioplatinum, vitallium, stainless steel, chromium cobalt, titanium, carbon and ruby (Glantz, 1998) have been fashioned into screws, hooks, baskets, meshes, plates, pins, rods, blades and staples in man’s attempts to find a material and technique which overcame the many biological obstacles he faced in trying to successfully and predictably restore the oral apparatus. Unfortunately, the majority of these attempts met with failure and often left the patient in worse shape than prior to the attempt due to the loss of bone from loose fixtures, chronic infection and multiple surgeries (Bobbio, 1973, Watzek and Blahert, 1996).

Modern implant dentistry had its beginning in the fifties when Professor Brånemark of Gothenberg, Sweden conducted his early research into the microvasculature of bone marrow in the rabbit’s fibula using optical chambers implanted endosseously. These studies led to the development of the principles of the Brånemark technique:

1. the use of commercially pure titanium
2. minimally traumatic surgery
3. a heal-in, unloaded period to minimise micro movement.

Brånemark states that “in order to provide predictable prognosis for the anchorage unit with an expected functional time of several decades meticulous tissue handling and care is the key to clinical success. This depends on precision in hardware composition and design of the
non-biologic implanted material and in software-how to handle it, install it, and use it for anchorage of the prosthetic construction."

Brånemark’s studies into the repair of osseous defects provide basic science knowledge on the mechanisms on the healing of bone and marrow to like tissues. He examined the short and long term effects of tissue injury from mechanical, chemical, thermal, and radiation forces as well as the effects of age, hormones, and temperature on healing tissues (Brånemark, 1985).

Out of his numerous studies came the principles espoused above. He was able to predictably implant commercially pure titanium fixtures into different parts of the skeleton, achieving a direct bone to implant interface with no soft tissue between bone and implant even when a trans-cutaneous abutment was connected (Brånemark et al, 1977). He found in his microvasculature studies little or no long-standing inflammatory processes to his micro-vascular chamber that was made of commercially pure titanium.

Animal studies demonstrated that proper differentiation to bone producing cells occurred if the trauma to the bone was minimised. If the trauma (mechanical or heat) exceeded this threshold, the tissues differentiated to a lower form and a fibrous interface was formed. This led to micro-movement and provided easier access to bacteria and ultimately led to the failure of the implant (Brånemark, 1985).

Osseointegration provides for direct bone to implant contact that is continually remodelling in response to the load placed upon it. The bone tissue must be handled in such a manner as to guarantee that the wounded bone is replaced during healing with the same highly differentiated tissue and not with a less well differentiated scar tissue.
With all surgical procedures, vascular disruption and cell death are inevitable. The key according to Brånemark is to minimise cell death and to allow adequate time for healing before heavy loading. His initial position was that a no load period was necessary for proper osseointegration, although this position seems to be changing in recent years.

Once established, osseointegration appears for the most part to be a long-term accomplishment (Adell et al, 1990, Henry et al, 1995, Zarb and Schmitt, 1996). Bone studies have shown that during healing and the first year of loading, patients experience some degree of bone loss. Subsequently, however a steady or stable state of bone is attained where bone is loss is less than 0.1 mm per year.

Success and Failure:

That osseointegration and its use for the replacement of missing teeth is a successful modality if carried out with care is without question at least over a thirty year period. Various authors have reported success rates of 97% in the edentulous mandible and 95% in the edentulous maxilla respectively, 88.6% and 94% in the anterior and 97.6% and 92.2% in the posterior in the partially edentulous mandible and maxilla and 100% in the single tooth replacement circumstance.

Many long term studies have confirmed these findings as well as the finding that bone loss after year one tends to be minimal, often in the range of 0.1mm per year. Most studies have also confirmed that failures generally occur prior to stage two surgery and that very few late failures (failures after loading) do occur.
Nature of Osseointegration:

Osseointegration is a descriptive term coined to describe the acceptance and integration of an alloplastic material into a host bone site for a prolonged period of time (Brånemark et al, 1977). The nature of this "integration" has been the subject of numerous studies.

It appears at this time that the nature of the integration is one of intimate contact between bone and the alloplastic material surface without an intervening fibrous layer. The nature of the contact appears to be one of physical micro and/or macroscopic (dependent on the nature of the surface texture of the implant) interdigitation of the bone matrix and cells into surface irregularities of the implant (Davies, 1996, 1997). There has been some speculation that various forms of chemical and/or electrical bonding occurs but these forces appear to be less important than the physical interlock.

Following surgical preparation and implantation bone grows toward and upon the implant in two ways. Distance osteogenesis occurs when the implant surface is not in contact with bone and osteogenesis occurs away from but towards the implant surface by appositional bone growth (Osborne and Newesley, 1980). This form of bone healing may increase the risk of allowing an intervening layer of cells and other forms of extra-cellular matrix to form between the implant surface and the bone and may be less desirable than contact osteogenesis (Steflick et al, 1998).

Contact osteogenesis occurs when the implant is placed in close contact with the bone surface (Osborne and Newesley, 1980). Initially the space between the implant surface and bone surface is filled with fibrin clot through which differentiating osteogenic cells migrate. As they migrate and differentiate some cells contact the surface of the implant and begin to lay down new or "de novo" bone. During this process, as with any wound, the clot undergoes retraction. It has been shown that more complex surfaces, topographically speaking, reduce the risk of clot
retraction away from the implant surface and therefore encourage a more successful
osseointegration (Davies, 1998). In addition, there is some evidence that some implant surfaces
(hydroxyappetite coated) increase the adsorption or chemical bonding potential of the implant
surfaces to the macromolecules of the wound healing environment (Moroni et al, 1994, Hanawa
et al, 1997).

Initially, the bone producing cells lay down a collagen free matrix layer consisting of
osteopontin and bone sialoprotein (Shen et al, 1993). This non-collagenous matrix then begins to
mineralise by nucleation and crystal growth (Davies et al, 1991a, b). At the same time but
slightly distant from the surface of the implant (0.5um.) collagen protein is secreted and begins
to organise and mineralise. This phenomenon occurs on many different types of implant surfaces
(both in terms of surface texture and chemical makeup). The nature of the “osseointegration”
may vary with the chemical nature of the implant surface as true “bone bonding” may occur with
certain bio-active materials (Matsuda and Davies, 1987). Following the initial healing phase an
ongoing process of remodelling takes place in response to stresses placed upon the implant and

As one examines the process of osseointegration of an implant, one sees that the process
is essentially a wound healing process in which an attempt is made to control the outcome. As
such this process is subject to the variables, which can affect any wound healing process. Drugs,
degree of trauma, hormone imbalances and systemic disease to name but a few are all factors
which one would predict to alter the delicate balance necessary to achieve optimal bone-implant
surface contact.
Factors Affecting Healing:

Numerous studies have attempted to elucidate those factors, which impact on the success/failure of osseointegrated implant systems. In general, systemic disease appears to have little or no impact on successful outcomes. (Smith et al, 1992, Ellies, 1993, Shernoff et al, 1994). Implants have been successfully used in patients undergoing glucocorticoid therapy (Cranin, 1991), with Sjögren syndrome (Payne et al, 1997), lichen planus, Erdheim Chester disease (Brahim et al, 1992) and with various congenital defects. Osteoporosis does not appear to negatively affect success (Dao et al, 1993).

Increased failure was noted when implants were place in bone that had been irradiated and into jaws of patients undergoing active chemotherapy. Success rates returned to normal if surgery was delayed till chemotherapy was completed (Wolfhaardt et al, 1996) and or if a hyperbaric oxygen chamber was employed in the case of radiation therapy (Parel et al, 1991, Kaneda and Takahashi, 1993, Taylor and Worthington, 1993).

Smoking has been well documented as having a negative impact on the absolute success/failure outcome as well as on the rate of bone loss over time (Bain and Moy, 1993, Lindquist et al, 1996, Habshe, 1999).

Various surgical techniques appear to play a role in implant success. Inexperience of the surgeon, lack of antibiotic prophylaxis and the use of short implants negatively affect the outcome (Sennerby and Roos, 1998). No effect on outcome was seen with the immediate placement of implants into non-infected sockets, with the use of angulated abutments (Balshi et al, 1997) or with the presence of exposed threads of the implant (Lekholm et al, 1996). Slightly higher failure rates are seen with a one stage surgical approach and with immediate loading
(Schnitman et al, 1997, Tarnow et al, 1997), although there is some controversy in the literature regarding this (Ericsson et al, 1994 Hermans et al, 1997).

Various augmentation techniques, involving the use of various materials and methods have been employed with osseointegrated implants placed both immediately and in a delayed fashion. A wide range of success/failure rates have been reported with the various techniques but it appears that implants can be placed into grafted bone both in an immediate and delayed fashion albeit with a somewhat less predictable result than into non-grafted sites (Sennerby and Roos, 1998).

In addition to surgical technique, location appears to be important as higher failure rates have been reported in the maxilla (10-20 %) (Adell et al, 1990, Zarb and Schmitt, 1996) than in the mandible (<5%) (Adell et al, 1990, Zarb and Schmitt, 1996). Several reports suggest higher failure rates in the posterior zones while others do not (Zarb and Schmitt, 1993, Avivi-Arber and Zarb, 1996, Wyatt and Zarb, 1998).

Bryant, in a very thorough review of the literature and in a study of age effects concluded that age does not impact osseointegrated success unless resorption has been so extensive as to prevent the placement of adequate numbers and sizes of implants (Bryant, 1998).

Furthermore it appears that bone quantity and quality may play a role in implant success, however, the findings are inconclusive due to the difficulties in conclusively defining and identifying quality and quantity (Jaffin and Berman, 1991, Jemt and Lekholm, 1995, Bryant, 1998).

As indicated earlier, failure rates among the general implant patient population have been very low. As such no single subgroup, with the exception of smokers; has been identified as being a group of individuals more at risk for short or long term failures or long term bone loss.
(Esposito, 1997). However, the research attempting to look at patient subgroups from the perspective of failure and bone loss has been limited. As a result of this initial research and the widespread impact of diabetes on health, a retrospective study to examine the diabetic implant patient subgroup was undertaken.

**Measures of Success:**

In evaluating any modality a valid method of evaluating success or failure must be developed. A first attempt at this was undertaken at a consensus conference held by the National Institutes of Health in 1979 (US Department of Health, 1980). Subsequently Albrektsson et al suggested that the success criteria be:

1. that an individual, unattached implant is immobile when tested clinically
2. that a radiograph does not demonstrate any evidence of peri-implant radiolucency
3. that vertical bone loss be less than 0.2mm annually following the implants first year of service
4. that an individual implant’s performance be characterised by an absence of persistent and/or irreversible signs and symptoms such as pain, infection, neuropathies, paresthesia, or violation of the mandibular canal
5. that in the context of the above, a success rate of 85% at the end of a five year observation period and 90% at the end of a ten year period be a minimum criterion for success.

(Albrektsson et al, 1986)

Smith and Zarb revised these outcome measures in 1989. They recommended that their criteria be applied when
1. Only osseointegrated implants should be evaluated with these criteria
2. The criteria apply to individual endosseous implants
3. At the time of testing the implants must have been under functional load
4. Implants which are beneath the mucosa and in a state of health in relation to the surrounding bone should preferable not be included in the evaluation but reported as complications
5. Complications of an iatrogenic nature that are not attributable to a problem with material or design should be considered separately when computing the percentage of success.

Their proposed criteria for success were:

1. The individual unattached implant is immobile when tested clinically
2. No evidence of peri-implant radiolucency is present on an undistorted radiograph
3. The mean vertical bone loss is less than 0.2mm annually after the first year of service
4. No persistent pain, discomfort, or infection is attributable to the implant
5. The implant design does not preclude the placement of a prosthesis with an appearance that is satisfactory to the patient and dentist.

Guckes et al in 1996 suggested a more comprehensive method of classification of treatment outcomes of implant therapy including:

1. Longevity/survival – implant fixture and prosthesis survival and treatment related morbidity/mortality
2. Physiologic impact- masticatory efficiency, bite force, maintenance of bone, effect of treatment on diet/nutrition
3. Physiologic impact- oro-facial body image, perceived quality of life, perceived satisfaction with prosthesis, self-esteem and interpersonal relations
4. Economic impact- direct costs of treatment, maintenance costs, indirect costs.

This entire question was revisited in 1998 at a symposium held at the University of Toronto entitled "Towards Optimising Treatment Outcomes for Dental Implants". After two days of meetings examining various aspects of implants and their successful use; an attempt was made to articulate a set of criteria/determinants which define successful implant supported prosthetic treatment. These criteria were published in the International Journal of Prosthetic Dentistry Vol. 11 1998. They are as follows:

1. Implant therapy is prescribed to resolve prosthodontic problems by permitting diverse prosthodontic treatments, which may in turn impact upon the economics of the service. Such prosthesis should meet the clinically evolved standards of function, comfort and aesthetics. They should allow for routine maintenance and should permit planned or unplanned revisions of the existing design. Treatment outcome success criteria for implant supported prosthesis should be assessed in the context of time dependent considerations for any required treatment.

2. Criteria for implant success apply to individual endosseous implants, and
   a. At the time of testing, the implants have been under functional load
   b. All implants under investigation must be accounted for
   c. Since a gold standard for mobility assessment is currently unavailable, the method employed must be specifically described in operative terms
   d. Radiographs to measure bone loss should be standard peri-apical films with specified reference points and angulations.
The success criteria comprise the following determinants:

1. The resultant implant support does not preclude the placement of a planned functional and aesthetic prosthesis that is satisfactory to both patient and dentist.

2. There is no pain, discomfort, altered sensation, or infection attributable to the implant.

3. Individual unattached implants are immobile when tested clinically.

4. The mean vertical bone loss is less than 0.2mm annually following the first year of function.
Hypothesis:

An analysis of the literature sited above suggests the following null hypothesis:

**Diabetes does not impact the outcome measures of Osseointegrated Bränemark Implants**
Objectives:

The objectives of this study are:

1. **To determine the success/failure ratio** of the diabetic subgroup of treated patients compared to matched non-diabetic controls.

2. **To determined the odds ratio** for failure with diabetic patients vs. controls

3. **To determine the rate of bone loss of the circum-implant bone** during the first year of loading within diabetic patients and to compare this rate to the rate seen in match non-diabetic controls.

4. **To determine if the diabetic effect is modulated** by other factors such as other systemic disease, other medications, smoking, bone quality and quantity, years edentulous, prosthesis type and opposing dentition.

5. **To determine the effects of the level of control** of the diabetic state on the outcome measures

6. **To examine the incidence of soft tissue, sensory and prosthetic complications** within the diabetic subgroup and to compare this incidence to the non-diabetic matched controls.
Material and Methods:

All 387 consecutively treated patients (to September 1999) in the Implant Prosthodontic Unit (IPU) at the Faculty of Dentistry of the University of Toronto were surveyed by way of a chart audit, and all self reported diabetics patients were identified. The treated patient population was comprised of those patients who:

1. demonstrated an inability to wear conventional removable or fixed prostheses;
2. had medical conditions which were stable and which permitted minor oral surgical procedures;
3. had sufficient bone to allow placement of a sufficient number and length of implants to ensure optimal prosthesis design;
4. had no history of substance abuse;
5. had realistic expectations with respect to aesthetic and functional outcomes;
6. had sufficient vertical interarch space to allow proper placement and restoration of the implant;
7. had no history of psychoses.

All patients treated within the IPU were informed that they were part of an on-going prospective study and agreed to participate. Written informed consent to participate in the on-going prospective study of implant therapy was signed by all participants prior to the commencement of therapy.

The medical history included patient completion of a standard health questionnaire to help determine the patient's past and present medical health status. Following completion of this form by the patient, a staff dentist conducted a patient interview to review this history at the screening appointment. The history was reviewed further by the treating surgeon at the surgical
consultation prior to placement of the implants. Additional notes were added in the daily notes of the patient to supplement the pre-printed form at the time of the interviews. The medical history was reviewed at each subsequent appointment.

All patients were treated with implant supported prostheses utilising standard surgical and prosthodontic techniques (Bränemark, 1982). The number of Bränemark implants placed, their length, design and sites of placement varied between patients. Traditionally four to six month healing protocols were observed between the two surgical stages. Dental speciality residents under staff supervision carried out each stage in a sterile environment under local anaesthetic. A few patients requested general anaesthetic. Several different analgesics were prescribed post surgically for all patients. The performing surgeon graded the bone quantity and quality at the time of surgery according to the Lekholm and Zarb classification (Lekholm and Zarb, 1985) and recorded their findings in the patient chart. Both dental speciality students and prosthodontic staff in the Implant Prosthodontic Unit carried out the prosthodontic treatment procedures. Standardised radiographs (Cox and Pharoah, 1986, Chaytor et al, 1991, Avivi-Arber, 1994) utilising a locating jig that controlled for angulation and focus to film distance were taken at the time of abutment placement. This was done to establish base-line bone heights and to confirm proper seating of the abutment (Cox and Pharoah, 1986, Chaytor et al, 1991). Following traditional prosthodontic adjustments, follow-up visits for monitoring purposes were scheduled, with some exceptions, on an annual basis. Such patient compliance was generally adhered to but a number of patients did not regularly attend annual recalls. Recall visits consisted of an updated medical history, a clinical examination, removal of the prosthesis whenever possible and standardised radiographs. Individual implants were examined to assess the health of the peri-implant tissues, implant mobility and the presence or absence of pain. Since it was not feasible to
remove all prostheses due to patient preference or the presence of a cemented final restoration, sequential radiographs for all patients were absent in some cases.

Identified diabetic patients were categorised according to the designations established by the WHO and the Canadian Diabetic Association as to Type 1, Type 2, Gestational or “Other” based on the treating dentist’s clinical notes in the context of each patient’s overall clinical history reports plus relevant physician information. All pertinent data, such as age, gender, age of onset of diabetes, method of control, other medical conditions, other medications, smoking habits, number and location of implants, type of prosthesis, opposing dentition, quality and quantity of bone, and years of partial or complete edentulism were recorded.

Each of these patients was then matched to two other non-diabetic implant patients from the patient population database of the IPU. The matching procedure used, identified the next consecutively treated patient who conformed to the matching criteria. Whenever an insufficient number of matches were identified going forward in the consecutively treated list of patients, the first match going in reverse through the treatment list was selected. This approach sought to address possible variations in surgical technique by limiting the control group to those patients operated on within a narrow time frame and treated by the same surgical group. Whenever possible, patients were matched with respect to age, gender, significant medical problems, number and location of implants, prosthesis type and smoking habits. All pertinent data collected for the diabetic patient population was also collected for the matched controls.

Proposed success criteria as delineated in 1998 at the Toronto consensus conference were applied to all patients and implants throughout the course of the patient’s treatment and follow-up period.(Zarb and Albrektsson, 1998) These results were recorded within the patient chart during the course of treatment by the treating dentists but were ignored by the investigator during
the matching procedure. Following matching the charts were reviewed and the various outcomes
were tabulated for each patient.

Following completion of the matching procedures, patients in both groups were contacted
and invited to attend a re-examination appointment in the IPU. At this visit, each patient’s
medical history was updated with particular attention paid to their diabetic status, age at
diagnosis, duration of diabetes, method of monitoring and control and the stability of their
condition over time. They were also asked about their smoking habits, plus other medical
conditions and medications taken. The number of years of partial or complete endentulism was
confirmed. The matched control group of patients was asked identical questions with the
exception of questions pertaining to the diabetic state. Conflicting information within the
medical history of two patients with respect to their diabetic state at treatment time resulted in
their being deleted from the diabetic group. Consequently, their controls were also deleted. Of
the potential 52 patients (several patients had both arches treated), a total of 18 patients could not
be recalled. These patients could not be recalled due to death (11), because of having moved
away from the area (6) or because of their refusal to attend a recall (1). Of the patients who had
died, 5 patient family members were interviewed with respect to the patient’s health records and
status of their oral health and implants prior to their death. The one patient who refused to attend
a recall did agree to discuss her oral and general health status in a telephone interview. The
remaining 34 patients were recalled for a compliance rate of 65.4%. When the patient family
interviews and the one patient interview are included in those recalled, the compliance rate
increases to 76.9%. While it is recognised that interviews do not substitute for an actual recall
examination, they did serve to confirm the patients’ health status and did lend some insight into
the status of the patients’ implant and prosthetic status.
Whenever possible each patient's prosthesis was removed to permit standardised periapical films of each individual implant. Circumimplant tissues were examined for signs of inflammation, swelling or suppuration. Individual implants were evaluated for mobility by applying a calibrated bucco-lingually force with the end of a mirror handle as well as percussed vertically to assess pain sensitivity. All abutment centre screws were torqued to a force of 20 Ncm via a torque wrench to determine if they were tight and to assess if this torquing action elicited a painful response. Any mobility or painful response to the induced torquing or tapping resulted in the implant being designated as a failure. The patient was also questioned with respect to the presence of any history of pain, paresthesia or any neurological disruptions. All procedures were conducted in harmony with the protocol established for the ongoing prospective study in which these patients participated.

The standardised radiographs were scanned into an Apple Macintosh Quadra 800 computer (Apple Canada Inc. 7495 Markham Rd., Markham, Ont. L3R 5G2) utilising a Microtek scanner (Microtek Scanmaker 35T, Microtek Lab Inc., 3715 Doolittle Dr., Redondo Beach, CA 90278). They were standardised as to contrast, and scale utilizing the public domain software NIH Image program 1.54 (Rasband, 1986, Wyatt, 1996). Measurements of bone height as measured from the shoulder of the abutment to the crest of the lowest plate of bone were obtained and recorded for both the mesial and distal of each implant. If the radiograph was unsatisfactory, no measurement was recorded. All measurements were repeated on two separate occasions and a mean was calculated between the two measurements for each site. This measurement was then utilised for statistical analysis of bone loss. If any measurement was more than two standard deviations different from the mean a third measurement was obtained and a new mean was calculated and recorded. All scanning procedures were carried out in a random
manner with the investigator blinded to the health status (i.e. diabetic or control) of the patient. Similarly, all calculations with respect to bone loss and rates of bone loss (slopes) were conducted without knowledge of the group to which the patient belonged.

**Data Analysis:**

All data were encoded within a Microsoft Excel chart according to a set of codes designed by the investigator (Appendix 1). These data were then transferred to the SPSS statistical program for analyses. Bivariate analyses consisted of Chi-square tests for nominal data and Student's t tests for interval data. Multivariate analyses consisted of multiple regression for continuous measures of bone loss and logistic regression predicting the risk of implant failure for diabetics and controls adjusting for the effect of potential confounders in the study. Logistic regression was also used to predict the risk of post-operative complications, such as soft tissue complications and sensory disruptions. Statistical tests were two-tailed and were conducted at the 5% significance level.
Results:

The medical histories of all consecutively treated patients of the IPU of the University of Toronto were examined to identify the diabetic patient population. A total of 387 charts were reviewed and 17 diabetic individuals, consisting of 5 males and 12 females, were identified. Of these, 2 patients, 1 female and 1 male, revealed conflicts within their self reported histories at the time of recall and were dropped from the study. The final group of 15 diabetics (4 males and 11 females) comprised 3.9% of the patient population in the IPU. This figure compares with the cited 4% of the general population with diabetes (Tan and MacLean, 1995). Thirteen (87%) of these patients were Type 2 diabetics while two (13%) were Type 1 diabetics. Here again, the percentages are similar to the ones quoted within the diabetic literature as the normal ratio (Tan and MacLean, 1995). The mean age of the diabetic group was 57.2 years, (range from 42 to 83 years) and for the control group was 55.7 years (range from 15 to 77 years).

Outcome: Success/Failure

Bivariate analyses consisting of Chi-square tests and t tests were utilised to examine the quality of matching between the diabetic and control subjects and to determine which factors would need to be controlled for in the linear and logistic multivariate analyses.

The Chi-square and t tests confirmed that the groups were properly matched for age, sex, years of edentulism and number of implants placed. In addition, the groups were matched for jaw and jaw zone containing the implants, prosthesis type, the opposing dentition and the length of the implants used (Table 1).

Differences were identified in the taking of other medication, other medical conditions, smoking habits, bone quantity and bone quality (Table 2). These factors were examined utilising linear and logistic regression modelling in an attempt to model their role in the outcome.
measures. The differences in bone quality and the presence other medical conditions were not significant between groups.

Table 1: Matched Characteristics between groups

<table>
<thead>
<tr>
<th>Subject’s Characteristic</th>
<th>Diabetic Group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>57.2±1.72*</td>
<td>55.7±1.26*</td>
<td>0.477</td>
</tr>
<tr>
<td>Percent Males</td>
<td>40.0% (24)</td>
<td>40.4% (46)</td>
<td>0.964</td>
</tr>
<tr>
<td></td>
<td>(36 f )</td>
<td>(68 f)</td>
<td></td>
</tr>
<tr>
<td>Mean Years Edentulous</td>
<td>11.29 ± 1.46*</td>
<td>12.09 ± 1.12*</td>
<td>0.690</td>
</tr>
<tr>
<td>Implant Number (right to left)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30.0% (18)</td>
<td>29.8% (34)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>26.75% (16)</td>
<td>26.3% (30)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16.7% (10)</td>
<td>14.9% (17)</td>
<td>0.992</td>
</tr>
<tr>
<td>4</td>
<td>11.7% (7)</td>
<td>13.2% (15)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>11.7% (7)</td>
<td>10.5% (12)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3.3% (2)</td>
<td>5.3% (6)</td>
<td></td>
</tr>
<tr>
<td>Jaw containing Implants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxilla</td>
<td>25.0% (15)</td>
<td>25.4% (29)</td>
<td>0.950</td>
</tr>
<tr>
<td>Mandible</td>
<td>74.6% (45)</td>
<td>74.6% (85)</td>
<td></td>
</tr>
<tr>
<td>Prosthesis Type ++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully edentulous-fixed</td>
<td>53.3% (32)</td>
<td>64.0% (73)</td>
<td></td>
</tr>
<tr>
<td>Fully edent.- overdent.</td>
<td>38.3% (23)</td>
<td>25.4% (29)</td>
<td>0.313</td>
</tr>
<tr>
<td>Partially edent.-fixed</td>
<td>3.3% (2)</td>
<td>6.1% (9)</td>
<td></td>
</tr>
<tr>
<td>Single tooth</td>
<td>5.0% (3)</td>
<td>4.4% (5)</td>
<td></td>
</tr>
<tr>
<td>Opposing Dentition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural</td>
<td>8.3% (5)</td>
<td>14.0% (16)</td>
<td>0.538</td>
</tr>
<tr>
<td>Part. edent.-removable</td>
<td>11.7% (7)</td>
<td>7.0% (8)</td>
<td></td>
</tr>
<tr>
<td>Complete denture</td>
<td>61.7% (37)</td>
<td>58.8% (67)</td>
<td></td>
</tr>
<tr>
<td>Complete fixed-natural or implant supported</td>
<td>18.3% (11)</td>
<td>20.2% (23)</td>
<td></td>
</tr>
<tr>
<td>Jaw Zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 1 (ant)</td>
<td>93.3% (56)</td>
<td>96.5% (110)</td>
<td>0.344</td>
</tr>
<tr>
<td>Zone 2 (post)</td>
<td>6.7% (4)</td>
<td>3.5% (4)</td>
<td></td>
</tr>
<tr>
<td>Length of Implant</td>
<td>11.53±.25mm*</td>
<td>12.12±.22mm*</td>
<td>0.094</td>
</tr>
</tbody>
</table>

Total # implants = 174  * = standard error  () = number of implants
Note: rounding may result in totals different than 100.0%
++ Note: Implant supported prostheses were never attached to natural teeth
### Table 2: Unmatched Characteristics Between Groups

<table>
<thead>
<tr>
<th>Subject’s Characteristic</th>
<th>Diabetic Group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1=yes, 2=no</td>
<td>53.3% (32)</td>
<td>71.1% (81)</td>
<td>0.020</td>
</tr>
<tr>
<td>Other Medical Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1=yes, 2=no</td>
<td>66.7% (40)</td>
<td>79.8% (89)</td>
<td>0.103</td>
</tr>
<tr>
<td>Smoking Habits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers (1)</td>
<td>53.3% (32)</td>
<td>31.6% (36)</td>
<td>0.005</td>
</tr>
<tr>
<td>Non Smokers (2)</td>
<td>46.7% (28)</td>
<td>68.4% (78)</td>
<td></td>
</tr>
<tr>
<td>Bone Quantity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>16.7% (10)</td>
<td>4.5% (5)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>11.7% (7)</td>
<td>31.5% (35)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>40.0% (24)</td>
<td>45.9% (51)</td>
<td>0.002</td>
</tr>
<tr>
<td>D</td>
<td>25.0% (15)</td>
<td>16.2% (18)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>6.7% (4)</td>
<td>1.8% (2)</td>
<td></td>
</tr>
<tr>
<td>Bone Quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15.0% (9)</td>
<td>11.7% (13)</td>
<td>0.104</td>
</tr>
<tr>
<td>2</td>
<td>41.7% (25)</td>
<td>58.6% (65)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>43.3% (26)</td>
<td>29.7% (33)</td>
<td></td>
</tr>
</tbody>
</table>

**Bone Quantity**- A(minimal to no resorption), B(Some Resorption of alveolus), C(complete resorption of alveolus), D(Some resorption of basal bone), E(Extreme resorption of basal bone)

**Bone Quality**- 1(primarily cortex), 2(thick cortex, dense cancellous), 3(thin cortex, dense cancellous)

**Note:** rounding may result in totals different than 100.0%

Identified failures occurred as follows: four (4) implants were lost in three diabetic patients and seven (7) implants were lost in five non-diabetic controls. Within the diabetic group the failures were split evenly between early and late losses (2 in each group), while within the non-diabetic controls more late losses were identified (2 early losses and 5 late losses). All failures occurred in the mandible in the diabetic group, while one third of the failures occurred in the maxilla in the control group. All failures in both groups occurred in the anterior zones. All failures occurred in fully edentulous patients in both groups with 50% of the failures occurring in cases in association with fixed prosthesis and 50% in patients treated with overdentures in the diabetic group. In the control group, 66% of the failures occurred in patients with fixed
prostheses, with balance in patients restored with overdentures. Within the diabetic group, 75% of the failures occurred in type 3 bone (thin cortex, dense cancellous bone) and 25% occurred in type 2 bone (thick cortex, dense cancellous bone). Within the control group, 33% of the failures occurred in type 1 bone (primarily cortex) and 67% were found in type 2 bone. In terms of bone quality, 25% of the failures seen in the diabetic group were seen in unresorbed alveolus (quantity A), and 75% in jaws with complete alveolar resorption but no basal bone resorption (quantity C). In contrast, 33% of failures in the control group occurred in quantity type B bone (some resorption of alveolus) and 67% occurred in type D bone (some resorption of basal bone). The majority of the failures occurred in both groups with implants 10mm in length (3 for diabetics and 6 for controls) with one 12mm failure in the control group, and one 13mm failure in the diabetic group. All differences within these factors were not found to be significant between groups by way of bivariate analyses.

Bivariate analysis to compare the outcome measure of success/failure between the diabetic group and control group was not found to be significant with a p-value of .905, and an Odds Ratio of 1.08 (95% C.I.= .303-3.852) (Table 3).

| Table 3. Unadjusted Odds Ratio for Implant Failure (Diabetics vs Controls) |
|-----------------|-----------------|-----------------|---|
|                  | Status without “other” |                 |   |
|                  | Failure          | No Failure       | Total |
| Diabetic vs      | Diabetic Group   |                 |     |
| Control          | % within group   |                 |     |
|                 | 4                | 55              | 59  |
|                 | 6.8%             | 93.2%           |     |
| Control Group    | % within group   |                 |     |
|                  | 7                | 104             | 111 |
|                  | 6.3%             | 93.7%           |     |
| Total            | Count            |                 |     |
|                  | % within study   |                 |     |
|                  | 11               | 159             | 170*|
|                  | 6.5%             | 93.5%           | 100%|

Odds Ratio = 1.08  95% Conf. Int. = .303-3.85,  p= 0.905
* 4 implants excluded, as they remained submerged and unused
Multivariate logistic regression analyses of the dependent variable success/failure which included group (diabetic and control), other medications taken (yes/no), other medical conditions (presence/absence), smoking habits (smoker vs. non smoker), bone quality (1-4), (Lekholm U and Zarb GA, 1985) and bone quantity (Lekholm U and Zarb GA, 1985) as independent variables was conducted. These analyses failed to identify any of the variables studied as having any significance in explaining implant failure in diabetic and control groups (Table 4).

Table 4: Results from Logistic Regression for Implant Failure

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group: Diabetic vs Control</td>
<td>1.32</td>
<td>.352-4.94</td>
<td>0.681</td>
</tr>
<tr>
<td>Other Medication (Yes vs No)</td>
<td>0.77</td>
<td>.162-3.62</td>
<td>0.736</td>
</tr>
<tr>
<td>Other Medical Conditions (Yes vs No)</td>
<td>5.132</td>
<td>.481-54.73</td>
<td>0.176</td>
</tr>
<tr>
<td>Smoking Habits (Yes vs No)</td>
<td>0.744</td>
<td>.311-1.78</td>
<td>0.506</td>
</tr>
<tr>
<td>Bone Quality</td>
<td>0.874</td>
<td>.305-2.51</td>
<td>0.802</td>
</tr>
<tr>
<td>Bone Quantity</td>
<td>1.593</td>
<td>.725-3.499</td>
<td>0.247</td>
</tr>
</tbody>
</table>

-2 Log Likelihood = 76.333; Chi-square = 4.768; df = 6; p = 0.574

Bivariate analysis of bone loss measurements to compare the means of the two groups with respect to age, number of years edentulous, pre-load bone measurements, and year one bone measurements found that there was no significant difference between the two groups with respect to these factors (Table 5).
Table 5: Mean (+ S.E.) Bone Loss Measurements (mm) for Diabetics and Controls by Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Diabetic group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preload</td>
<td>1.18±0.08</td>
<td>1.11±0.05</td>
<td>0.399</td>
</tr>
<tr>
<td>Year 1</td>
<td>1.44±0.10</td>
<td>1.28±0.11</td>
<td>0.270</td>
</tr>
</tbody>
</table>

Examination of the mesial and distal bone measurements and the rates of bone loss in any period studied by way of *t*-tests did not demonstrate any significant difference between these measurements. As a result the mesial and distal measurements were both utilised in determining the averages which were used for analysis of bone loss. Mann-Whitney testing confirmed these findings. Analysis of the differences in mean bone loss between groups by year was found to be significantly different only in year one of loading. However, analysis of the mean of the slopes of bone loss for years 1-5, 5-8, 9-12 and overall, demonstrated no significant difference between groups (Table 6).

Table 6: Mean (+ S.E.) of Bone Loss for Diabetics and Controls

<table>
<thead>
<tr>
<th>Year</th>
<th>Diabetic Group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone loss during year 1</td>
<td>0.25±0.07</td>
<td>0.06±0.04</td>
<td>0.018</td>
</tr>
<tr>
<td>Slope of bone loss years 1-5</td>
<td>0.09±0.06</td>
<td>0.24±0.14</td>
<td>0.349</td>
</tr>
<tr>
<td>Slope of bone loss years 5-8</td>
<td>-0.02±0.03</td>
<td>0.02±0.04</td>
<td>0.529</td>
</tr>
<tr>
<td>Slope of bone loss years 9-12</td>
<td>0.10±0.05</td>
<td>0.05±0.04</td>
<td>0.458</td>
</tr>
<tr>
<td>Overall slope of bone loss</td>
<td>0.12±0.05</td>
<td>0.13±0.11</td>
<td>0.955</td>
</tr>
</tbody>
</table>

Multiple regression analysis of the bone loss in the first year was conducted to examine the groups in the context of unmatched factors: other medications taken, other medical
conditions, smoking habits, bone quality and bone quantity. These analyses found a significant difference between groups but did not identify diabetes as being significant in predicting the outcome of more bone loss. Smokers and those individuals with greater bone quantity were found to have a greater risk of bone loss. This model was found to be highly significant (Table 7).

**Table 7: Multiple Regression Model for Bone Loss in the first year of Implant Loading**

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1.542</td>
<td>.390</td>
<td>0.000</td>
</tr>
<tr>
<td>Diabetic vs control</td>
<td>-0.021</td>
<td>.124</td>
<td>0.865</td>
</tr>
<tr>
<td>Other Medical Conditions – yes vs no</td>
<td>0.149</td>
<td>.121</td>
<td>0.223</td>
</tr>
<tr>
<td>Other Medications taken - other meds taken vs no other meds taken</td>
<td>-0.188</td>
<td>.123</td>
<td>0.131</td>
</tr>
<tr>
<td>Smoking Habits – smoker (1) vs non-smoker (2)</td>
<td>-0.268</td>
<td>.133</td>
<td>0.021</td>
</tr>
<tr>
<td>Bone Quantity – Lekholm and Zarb</td>
<td>-0.150</td>
<td>.048</td>
<td>0.003</td>
</tr>
<tr>
<td>Bone Quality – Lekholm and Zarb</td>
<td>-0.115</td>
<td>.070</td>
<td>0.104</td>
</tr>
</tbody>
</table>

\[ F = 5.044; P < 0.001; \text{ Adj. R square } = 0.237 \]

Bivariate analyses of the various complications associated with implant treatment was then conducted (Table 8). These complications were divided into soft tissue complications, sensory disruptions, such as pain and paresthesia, and prosthetic complications.

Chi-square analysis found no significant difference between the diabetic and control group with respect to soft tissue complications. With respect to sensory disruptions, Chi-square analysis identified a significant difference between groups with respect to both the incidence of
paresthesia and the report of post-operative pain. The differences were highly significant with the diabetics reporting paresthesia in more patients, 10.0% vs 0.9% for controls, and the control patients reporting more post operative pain, 28.3% vs. 10.0% for diabetics. With respect to prosthodontic complications, no significant difference was found between groups; however, the control group experienced more gold screw fractures than did the diabetic group. The total percentage of subjects experiencing complications was virtually the same, with diabetics having a rate of 20.0% and controls having a rate of 21.2%.

Table 8: Complications

<table>
<thead>
<tr>
<th>Complication Type</th>
<th>Diabetic Group n=60</th>
<th>Control Group n=114</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft Tissue (yes vs no)</td>
<td>35.0% (21)</td>
<td>44.2% (50)</td>
<td>0.239</td>
</tr>
<tr>
<td>Sensory (yes vs no) Paresthesia</td>
<td>10.0% (6)</td>
<td>0.9% (1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>10.0% (6)</td>
<td>28.3% (32)</td>
<td></td>
</tr>
<tr>
<td>Prosthodontic (yes vs no) Gold screw fracture</td>
<td>0.0% (0)</td>
<td>5.3% (6)</td>
<td>0.273</td>
</tr>
<tr>
<td>Abutment screw fracture</td>
<td>5.0% (3)</td>
<td>2.7% (3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15.0% (9)</td>
<td>13.3% (15)</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square test; () = count

Multivariate analyses were conducted using logistic regression for the outcome soft tissue complications (yes vs no) that included the factors: group, medical history, other medication, smoking bone quality, and bone quantity as independent variables (Table 9). Of the factors tested, medication taken, and bone quantity proved to be significant. The taking of other medications and reduced bone quantity were associated with an increased likelihood of soft tissue complications. Group type was not found to be significant.
Table 9: Logistic Regression Model for Soft Tissue Complications

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group – Diabetic vs Control</td>
<td>1.32</td>
<td>0.56-3.03</td>
<td>0.511</td>
</tr>
<tr>
<td>Other Medications taken - other meds taken vs no other meds taken</td>
<td>0.10</td>
<td>0.03-0.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking Habits- Smoker (1) vs non-smoker (2)</td>
<td>0.61</td>
<td>0.33-1.11</td>
<td>0.108</td>
</tr>
<tr>
<td>Bone Quality A</td>
<td>3.13</td>
<td>1.70-5.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bone Quality B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Quality C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Quality D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Quality E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Quality - 1(primarily cortex), 2(thick cortex, dense cancellous), 3(thin cortex, dense cancellous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Quality - 4</td>
<td>0.55</td>
<td>0.29-1.03</td>
<td>0.063</td>
</tr>
<tr>
<td>Other medical conditions (yes vs no)</td>
<td>0.36</td>
<td>0.12-1.04</td>
<td>0.060</td>
</tr>
</tbody>
</table>

-2 Log Likelihood = 166.854; Chi-square = 64.183; df = 6; P < 0.001
Bone Quantity- A(minimal to no resorption), B(Some Resorption of alveolus), C(complete resorption of alveolus), D(Some resorption of basal bone), E(Extreme resorption of basal bone)

Multivariate analysis of sensory complications found that paresthesia was more likely in smokers and those with lesser bone quantity. Group, i.e. diabetic vs. control, was not significant in the multivariate modelling (Table 10). Pain was found more often in those in the control group. No other factor was significant (Table 11).
Table 10: Logistic Regression Model for Sensory Complication-Paresthesia

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group – diabetic vs control</td>
<td>1.247</td>
<td>0.043-36.46</td>
<td>0.898</td>
</tr>
<tr>
<td>Smoking Habits-Smoker (1) vs non-smoker (2)</td>
<td>0.014</td>
<td>0.00-0.35</td>
<td>0.009</td>
</tr>
<tr>
<td>Bone Quantity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12.79</td>
<td>1.38-118.26</td>
<td>0.025</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-2 Log Likelihood = 28.043: Chi-square = 26.695; df = 3; P < 0.001
Bone Quantity-A(unresorbed), B(Some Resorption of alveolus), C(complete resorption of alveolus), D(Some resorption of basal bone), E(Extreme resorption of basal bone)

Table 11: Logistic Regression Model for Sensory Complication-Pain

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-diabetic(1) vs control(2)</td>
<td>3.63</td>
<td>1.43-9.24</td>
<td>0.007</td>
</tr>
<tr>
<td>Other medication taken (yes vs no)</td>
<td>1.58</td>
<td>.75-3.33</td>
<td>0.228</td>
</tr>
<tr>
<td>Bone quality-1 (primarily cortex), 2(thick cortex, dense cancellous), 3(thin cortex, dense cancellous)</td>
<td>0.69</td>
<td>0.40-1.17</td>
<td>0.169</td>
</tr>
</tbody>
</table>

-2 Log Likelihood = 214.198: Chi-square = 11.044; df = 3; P = 0.012
Bone Quality- 1(primarily cortex), 2(thick cortex, dense cancellous), 3(thin cortex, dense cancellous)

A bivariate analysis was also conducted to compare the health outcome of the two groups (diabetic and control) (Table 12). Of the diabetics, 38.9% (n=7) had passed away during the study period compared to only 8.8% (n=3) of the control group. A Chi-square value of 6.849 with 1 degrees of freedom indicated a highly significant difference, p value = 0.009.
Table 12: Health Status of Diabetic and Non-Diabetic Control Patients

<table>
<thead>
<tr>
<th></th>
<th>Health Status</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Deceased</td>
<td>Living</td>
<td>Total</td>
</tr>
<tr>
<td>Diabetic</td>
<td>Count</td>
<td>7</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>% within Diabetic vs Control</td>
<td>28.3%</td>
<td>68.3%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Control</td>
<td>Count</td>
<td>3</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>% within Diabetic vs Control</td>
<td>1.8%</td>
<td>93.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>10</td>
<td>42</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>% within Diabetic vs Control</td>
<td>10.9%</td>
<td>84.5%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Chi-square = 6.849; df = 1; p = 0.009
Odds Ratio = 6.58; Confidence Interval = 1.44-29.99
Note: analysis conducted at the patient level
**Discussion:**

Diabetes is a metabolic disorder, which affects numerous body systems at the organ, cellular and molecular level, including the body’s cardio-vascular, renal, neurological, immune and wound healing systems. Successful implant therapy depends on numerous determinants including a successful wound healing response to the surgical wound induced during implant placement. Consequently, any alteration of this biological process by excessive surgical trauma, infection or metabolic upset may adversely affect treatment outcomes.

The patient with diabetes mellitus who undergoes surgery is vulnerable to infection as a result of compromised humoral and cellular immune responses. Altered polymorphonuclear neutrophil cell functions: altered chemotaxis, activation, adherence, reduced killing ability (Cutler et al, 1991), increased superoxide production, reduced surface charge and reduced intracellular lysozyme (Grant-Theule, 1996), as well as an increased production of elastase and collagenase (Ramamurthy et al, 1983), can increase both the risk of tissue damage and the risk of microorganisms invading the host tissues.

Diabetics have also been found to have altered humoral factors within their immune system. It has been shown that a chemotactic inhibitory factor exists in the sera of diabetic patients as well as increased levels of circulating immune complexes. These circulating immune complexes are believed to mediate tissue damage (Grant-Theule, 1996). Additionally diabetics have an altered C3 response to microbial challenge as the binding of glucose to this molecule inhibits its ability to bind to the surface of the invading micro-organism and as a result chemotaxis, adhesion and phagocytosis by PMNs is altered (Annil et al, 1990).

Treatment outcomes in the diabetic group of patients in this study suggest that infection did not impact upon the selected outcome criteria. No reports of infection during the healing
phase or the post-surgical, prosthetic insertion phase were noted and in fact it was found that the diabetic group and the control group had similar numbers of soft tissue complications. This is likely the result of the surgical protocol employed: a sterile surgical approach plus antibiotic coverage during surgery and the early recovery period. This finding reflects those of Fernandez et al, 1997 who reported on the risk of infection in total hip replacement. He also found that diabetes was not a risk factor for increased infection and noted that proper care of the wound and the use of antibiotic prophylaxis acted synergistically to reduce infection. (Fernandez, 1997)

Diabetic patients have also been found to have an altered wound healing response, as well as to demonstrate a wide range of defects that alter the healing response. The latter include decreased perfusion and oxygen tension as a result of microangiopathy; increased collagenase and elastase activity as a result of increased proinflammatory cytokine production by altered monocyte phenotypes, and abnormalities in the synthesis and maturation of collagen.

The macrophage, a key element in normal wound healing, (Barbul and Regan, 1995, Steed, 1997) present with altered phenotypes in diabetic patients. These altered phenotypes result in an altered inflammatory response phase, altered cytokine production, altered growth factor production and reduced nitric oxide production. Many of these changes are the result of the presence of advanced glycation endproducts (AGE). (Iacopino, 1995) and result in an alteration in the delicate balance of catabolism and metabolism present in wound healing, favouring the catabolic processes. The net result is altered and delayed healing of the wound. (Iacopino, 1995, Schaffer et al, 1997).

The reported success rate of 93.2% within the diabetic group in this study appears to be in agreement with the results reported by Shernoff et al, 1994 and Balshi et al, 1999. These authors reported success rates of 93.7% and 94.3% respectively. In addition, Ardekian, 2000
recently reported in abstract form, success rates of between 93-95% after three years. In contrast, Smith et al, 1992 and Kapur et al, 1998 reported no failures within their diabetic group. However, differences within these studies’ designs demand consideration (Figure 2).

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design, Prosthesis Type</th>
<th>Patient #</th>
<th>Follow-up Period</th>
<th>Type of Implants</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al 1992</td>
<td>Retrospective Multiple prosthesis designs Designs not specified for diabetic type ****</td>
<td>4 Type 1 1 Type 2</td>
<td>Healing-up to 4.5 years</td>
<td>Brånemark</td>
<td>100%</td>
<td>No controls, No recall Small sample, short follow-up</td>
</tr>
<tr>
<td>Shernoff et al 1994</td>
<td>Prospective Overdentures ****</td>
<td>89 Type 2</td>
<td>1 year</td>
<td>Multiple- Dentsply, Brånemark , Interpore</td>
<td>93.7%</td>
<td>No control Multicentre(13), short follow-up, multiple types</td>
</tr>
<tr>
<td>Kapur et al 1998</td>
<td>Prospective Overdentures Own success criteria</td>
<td>50 Type 1 39 Type 2</td>
<td>24 mons. Including healing period</td>
<td>IMZ</td>
<td>100%</td>
<td>No controls, tight diabetic screening and monitoring Short follow-up</td>
</tr>
<tr>
<td>Balshi et al. 1999</td>
<td>Retrospective Unloaded ****</td>
<td>34 Type not specified</td>
<td>Healing-up to 15.5 mons.</td>
<td>Brånemark</td>
<td>94.3%</td>
<td>No controls No recall Several techniques- immediate and conventional</td>
</tr>
<tr>
<td>Accursi et al 2000</td>
<td>Retrospective 1998 Zarb and Albrektsson success criteria applied</td>
<td>13 Type 2 2 Type 1</td>
<td>1-17 yrs, including healing period</td>
<td>Brånemark</td>
<td>93.2%</td>
<td>2 matched controls, Recalls conducted, no diabetic screening, long follow-up, bone studied</td>
</tr>
</tbody>
</table>

**** Success criteria not stated
Shernoff et al studied a group of 89 type 2 diabetic patients treated with overdentures supported by two root form implants from three different manufacturers (Dentsply, Noblepharma and Interpore). The patients were followed for a period of one year. Four implants were mobile at stage two surgery and a further nine implants failed over the ensuing year. Although they do not discuss the difference in outcomes with different manufacturer's it appears from the raw data that the greatest number of failures occurred within the Dentsply group followed by the Noblepharma group. They report that shorter implants failed more frequently. Several problems exist with this study. The use of multiple implant types and a failure to control for this fundamental factor are significant shortcomings of this study. Each implant manufacturer has a different manufacturing technique and as such the resultant implant presents with a different surface configuration. As surface texture has a significant effect on osseointegration and hence outcome; interpretation of their results is difficult. The very short follow-up period, the lack of matched controls, and the use of 13 treatment centres also make it difficult to draw meaningful conclusions from their study. Similar comments can be made concerning the Ardekian study as these investigators also had multiple surgical approaches, lacked controls, and followed their patients only for periods up to three years.

Smith et al and Balshi et al both present retrospective studies exclusively utilising Bränemark implants; however, each study has several significant difficulties. Smith et al’s study involved only five diabetic patients, had a short follow-up period, did not involve a patient recall at the time of the study and did not utilise matched controls. Balshi’s study population was larger (34 patients) but the investigators failed to specify the diabetic type, and only followed their patients for periods up to 15.5 months (healing period). They also utilised multiple surgical techniques involving grafting procedures, immediate placement into sockets as well as the
conventional surgical approach. Again no matched control group was utilised. Interpretation of their results in light of these deficiencies again renders the results difficult to interpret. All of the above studies did not specify the criteria that they utilised in evaluating success.

The Kapur study (Kapur et al, 1998) was undertaken to examine patient satisfaction with implant supported over-dentures compared to conventional dentures in diabetic patients. He reported virtually as an aside on the failure rate of the implants and on the bone loss patterns. While the study was well designed for the purpose intended, it lacked normal controls, had a short follow-up of only two years and introduced into the patients' routine a tight diabetic monitoring regimen and a strict oral hygiene follow-up program. Both of the latter two shortcomings can be viewed as interventions, which may have significantly altered the outcome by altering the patients' level of diabetic control and their degree of oral self care. Similarly the investigators excluded any patients with glycosylated hemoglobin > 13.0% where as my study accepted any diabetic who was ambulatory and who reported that they were in "good control". Kapur's selection criteria may therefore have biased his results by excluding diabetic patients who might reasonably be expected to present for treatment in a normal dental office. In addition, no recognised criteria for success was utilised in evaluating the success or failure of the implant, thereby creating confusion regarding what he deemed to be a successful outcome.

Esposito in a recent detailed analysis of implant failures concluded that early failures were most likely attributable to infection, impaired healing ability of the recipient site or disruption of a weak bone to implant interface. Late losses seemed to be caused by overload in relation to host characteristics or deep infection. (Esposito et al, 1997,1998a,1998b) Our results appear to support his conclusion based on the fact that within the diabetic group 50% of the failures occurred as early failures while within the control group, 29% of the failures were early
losses. These findings support the concept that diabetes disrupts the normal healing occurring following successful implant surgery.

Animal studies using a Streptozotocin induced diabetic rat model by a variety of groups in different labs have found that the amount of bone formed was less in the diabetic rat than the control and that the amount of bone to implant contact was also reduced (Takeshita et al, 1997, Iyama et al, 1997, Takeshita et al, 1998). Nevins et al reported similar amounts of bone formed between diabetic and control animals and less bone-implant contact in the diabetic model (Nevins et al, 1998). McCracken et al in a very recent paper reported an increased volume of bone production but reduced bone-implant contact (McCracken et al, 2000). Fiorellini et al found that insulin helped to upregulate the amount of bone formed around the implant but that the amount of bone-implant contact remained significantly less than the controls (Fiorellini et al, 1999). These animal studies appear to support the conclusions drawn by Esposito with respect to the impact of impaired healing of the recipient site and the resultant reduced bone-implant contact. They may also provide a clue to the difference seen in early loss rate between diabetics and control within this study.

Reduced bone-implant contact may indicate a poorer healing response and may predict a reduced ability of the implant to withstand bacterial and load challenges. If the lack of bone-implant contact is carried to the extreme, osseointegration would be deemed to have failed and the implant would be found to be mobile at stage two surgery. It seems reasonable to postulate that an implant demonstrating reduced bone-implant contact may be less able to withstand functional stresses placed upon it during the healing phase. Further breakdown of the circum-implant bone could therefore ensue and this could result in a loosening of the implant and its ultimate failure. Furthermore, this increased implant mobility within its bony socket could
possibly increase the potential for bacterial invasion; however, no report of clinically observed circum-implant infection was found in any of the diabetic patients in this study.

In summary, these observations do not suggest a bacterial cause of failure. It appears that the altered healing response seen in the diabetic patient results from less circum-implant bone formation and less bone-implant contact. This renders the implant less “well integrated” from a quantitative point of view and presumably less resistant to micromovement and more prone to early failure.

The diabetic group was found to lose more bone during the first year of function than was the control group. Mean bone loss measured in the diabetic group in year one was 0.25 ± 0.07mm in contrast to the smaller bone loss (0.06±0.03mm) measured in the control group. These measurements are in agreement with the bone loss of 0.21mm reported for diabetics by Kapur et al in the only other study reporting on the relationship between diabetes and crestal bone loss. He also found a reduction in bone loss rate after year one of loading. It should however be emphasised that the latter study did not report on any non-diabetic controls (Kapur et al, 1998). Numerous other studies have reported crestal bone loss ranging from near zero to 0.65 mm in the first year of loading. All have reported a decline in the rate of bone loss in the following years to rates of less than 0.1mm per year. This reduction in bone loss indicates a stabilisation in the rate of turnover of the crestal bone (Adell et al, 1981, Lindquist et al, 1988, Zarb and Scmitt, 1990, Chaytor et al, 1991, Avivi-Arber and Zarb, 1996, Lindquist et al, 1997, Wyatt and Zarb, 1998, Bryant, 1998). However all of these studies with the exception of the Lindquist et al study, which examined the influence of smoking on crestal bone loss, dealt with a mixed group of patients and did not attempt to account for such factors as diabetes. It is therefore
difficult to make direct comparisons in terms of absolute values but certainly the trends for bone loss patterns within diabetics remain similar to those seen in the previous mixed studies.

Animal studies found less bone formation and less bone-implant contact within the both the uncontrolled and controlled diabetic experimental groups. As stated earlier, these findings suggest that such implants are less able to withstand mechanical stress placed upon them after loading with a resultant vulnerability to micro-movement. This could in turn result in an increased loss of bone at the bone crest.

Furthermore, once the implant is loaded, the circum-implant bone will attempt to respond to the stresses received by it. It seems reasonable to presume that the bone responds with increased remodelling which results in an increased turnover of the circum-implant bone. If the implant has less bone contact and less bone surrounding it, as seen in the diabetic rat model, a need for a greater degree of remodelling to enable the implant to withstand the functional stresses placed upon it may be required. As a result, a greater rate of crestal bone change may occur until the bone has re-organised sufficiently to withstand these functional stresses. Once the bone has responded to the forces at play upon it, the rate of remodelling likely slows and the rate of bone loss returns to that seen in normal patients. These views are lent credence by the findings of Forrest G et al 1998, who reported that diabetics required longer inpatient rehabilitation than non-diabetic patients following hip and knee arthroplasty. This area clearly requires further study.

**Soft Tissue Complications:**

Soft tissue complications were similar in number in both the diabetic and control patients. The frequency of these complications was seen to increase with a reduction in the quantity of bone present and with the taking of other medications. In agreement with the many reports on the
health of gingiva surrounding implants; these complications both in the diabetic and control group were of a minor nature and involved redness, bleeding or minor swelling. All resolved with improved oral hygiene (Apse et al, 1991, Van Steenberghe et al, 1993, Buser et al, 1994, Merickse-Stern et al, 1994). This appears to be a contradiction to the reports of increased gingival and periodontal problems within the diabetic dentulous population. One can speculate that the staff dentists of the IPU were particularly diligent about stressing the importance of good oral hygiene in the maintenance of healthy circum-implant tissues. Additionally, the diabetic group, as a result of education within the diabetic population may have been more aware of the risk of developing periodontal problems due their diabetes. As a result of their desire to have successful 'new teeth', diabetic patients may have been more highly motivated to maintain their oral self-care.

The finding that patients with less bone quantity had an increase in the number of soft tissue complications is also at odds with the findings of other groups. Other authors have reported that the placement of implants into unattached mucosa does not result in an increase in the incidence of soft tissue complications when compared to those placed into attached mucosa (Zarb and Schmitt, 1996). The explanation of this difference is unknown but could certainly be related to the smaller sample size in this study.

Many medications such as corticosteroids, hydrogen peroxide, Dilantin, calcium channel blockers, tetracyclines and hormones have been reported to have an impact on gingival and periodontal health (Ciancio, 1996). This study did not attempt to categorize the medications taken by the IPU patients and as such was unable to determine which medications may have contributed to any observed changes. It should be underscored that soft tissue changes may also be the result of altered behaviour, altered plaque composition, altered tissue responses or altered
gingival crevicular fluid, all of which can be effects of medications. The interplay between the diverse medications taken by dental patients and their possible intra-oral manifestations in patients with dental implants appears to be an area, which deserves study.

**Sensory Complications:**

The sensory complications encountered present an interesting finding. Diabetics were found to experience more paresthesia and less pain post-operatively in the bivariate analysis when compared to the control group. This finding may be explained by the fact that one of the major complications of diabetes is diabetic neuropathy (Can. Diabetes. Assoc. 1992, 1998, Sculley, 1998). Diabetic neuropathy can present with a wide variety of symptoms ranging from severely reduced sensibility all the way to continuous severe pain. It could be postulated that the responsiveness and reparative abilities of the peripheral nerves had already been reduced by the diabetic state, rendering the various nerves more easily damaged with a slower and less predictable recovery ability. These changes would result in an increase in the incidence of post-operative paresthesia. Furthermore, one cannot discount the possibility of neurologic disruption being present in the diabetic group prior to the placement of the implants. Subsequently, the surgical procedure and the post-operative questioning drew the attention of the patient to this problem with the resultant increased incidence of paresthesia being reported. Since neurological testing was not undertaken prior to treatment this hypothesis suggests the merits of further study. The reverse of the above argument might explain the fact that the control group experienced more postoperative pain.

The multivariate analysis of factors influencing sensory complications revealed that smokers, and those patients with poorer bone quantity were more likely to experience paresthesia post-operatively. Group (diabetic vs. control) was not found to be significant. Group (diabetic vs. control) was not found to be significant.
control) however, was the only significant factor in predicting postoperative pain, with controls reporting a higher frequency. A reduction in the quantity of bone seems more likely to expose the nerve tissue to damage during the surgical procedure. Smoking, due to the presence of numerous toxins may reduce the sensitivity of the neural tissue and may also render the nerve tissue less able to withstand or to recover from the impact of surgery. These arguments are speculative and based on a small number of reported complications. Much more study involving proper controls and pre-operative testing is required before attempting to draw any definite conclusions.

**Prosthetic Complications:**

Prosthetic complications were essentially the same for the diabetic and control groups except that control patients broke more gold screws. The abutment screw fractures involved one patient who was a severe bruxer who fractured abutment screws even before the prosthesis could be placed since she was bruxing directly on the abutments. Her fixed prosthesis was replaced with an overdenture and has been problem free ever since. The gold screw fractures recorded involved two patients in the control group. Prosthetic problems with the various prostheses were identical between groups. These findings are not surprising given that diabetes is unlikely to affect the mechanical elements of the restoration or the patients' functional demands placed upon them, plus the fact that the groups were not different with respect to prosthesis type and opposing arch type. Any noted minor differences in the incidence of prosthetic complications were due to unique problems associated with very few patients or their prostheses.

It is readily conceded that this study involved a small sample size. Nonetheless, it is interesting that the death rate within our diabetic group was substantially higher than that found within the control group. This finding reflects what is reported in the diabetic literature and is
believed to be a function of the long-term sequelae of diabetes. Gu et al in 1998 reported higher death rates for diabetics compared to non-diabetics for all age, sex and race groups. The relative risk of death reported was elevated for all major causes of death except neoplasm. Median life expectancy was 4-8 years lower for diabetics compared to non-diabetics (Gu et al, 1998).

This study has inherent in it several problems which need to be recognised. They are as follows:

1. **Small sample size** - An attempt to overcome this problem was made by closely matching each diabetic with two controls. By increasing the size of the control group the profile of this group became better defined and as such difference between groups, even if the study group was relatively small would have a greater chance of being detected.

2. **Retrospective in nature**- This form of study is perhaps the lowest in the clinical study hierarchy as it is dependant on the accuracy of the patient records of information gathered by a variety of clinicians not aware of the details which would later be significant in the study. This leads to missing information and perhaps less than ideal information. Future matched control prospective studies would strengthen our knowledge in this area.

3. **Impact of Diabetic metabolic control not evaluated** – This is a planned extension of this study and will be conducted by way of a survey to treating physicians to
   (a) Assess the difference between the patient’s view of his control with that of the treating physician’s, with that which is indicated by the objective lab results.
   (b) Factor in the impact of the level of control and method of control with the outcomes to determine the role of these factors on the outcome measures.
In summary, diabetes mellitus is a common metabolic disorder affecting 4% of the general population. It has a widespread impact on the systemic health of the affected individual at the system, organ, and cellular and molecular levels. This preliminary study determined that outcome measures of success of Brånemark osseointegrated implants in diabetic patients are affected by their disorder both by the diabetes itself and when in combination with other host factors.

The degree of impact, while significant, should not lead a clinician to reject ambulatory, controlled diabetics from receiving osseointegrated implant therapy. The value of this study lies in improving the ability of the clinician to properly inform his diabetic patients of the risks and benefits of the chosen therapy so as to better allow such patients to make a more informed choice about the therapy they are about to receive. While this preliminary study offers valuable information regarding the treatment planning of diabetic patients requiring implant-supported prostheses it seems prudent to suggest:

- Further prospective studies possibly in the form of a multi-centre study, involving larger patient numbers with close monitoring of the diabetic patients with respect to their degree of diabetic control in order that the correlation between control and the various outcome measures may be ascertained.
- Animal studies involving controlled and uncontrolled diabetic models to attempt to determine the mechanisms at play in the tissues surrounding the osseointegrated implant.
Conclusions:

Within the limits of this study’s research design the following conclusions may be drawn:

1. Diabetic patients are not likely to experience more overall implant failures than non-diabetic control patients; however, failures in the diabetic group occurred more frequently as early failures (between stage 1 and stage 2 surgery) than in the non-diabetic control group.

2. Diabetic patients are more likely to demonstrate an increased loss of bone during the first year of implant loading when compared to non-diabetic controls. This difference in rate appears to disappear in subsequent years and matches reported levels for studied non-diabetic population groups. Smokers and patients with more bone quantity at the time of implant placement have a tendency to lose more bone around the implant during the first year of implant function.

3. Diabetic patients experienced similar numbers of soft tissue complications when compared to controls. Soft tissue complications in both groups were of a minor nature and easily resolved. Less bone quantity and the taking of other medications may contribute to increased soft tissue complication frequency.

4. Diabetics reported a higher incidence of paresthesia and less postoperative pain than non-diabetic controls.

5. Findings suggest that ambulatory Diabetes Mellitus patients are suitable candidates for treatment with osseointegrated Brånemark implants.
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