Body Composition of Infants with Gastroschisis Assessed by Air Displacement Plethysmography

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Nutritional Sciences
University of Toronto

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Abstract

**Background:** Measuring body composition (BC) in infants enables monitoring their growth pattern. Air displacement plethysmography (ADP), a BC technique that is practical for infants, but has not been adequately assessed in different infant populations.

**Objective:** To demonstrate the suitability of the ADP in a high-risk population and to evaluate their BC.

**Methodology:** The study was observational; subjects were recruited from the Hospital for Sick Children. A total of 12 Infants ≥ 33 weeks corrected gestational age at birth, diagnosed with gastroschisis, were studied. BC was measured post-surgery and a month thereafter.

**Results:** fat mass (FM) did not show a significant difference in our study group compared to healthy infants at both measurements. However, fat free mass (FFM) was significantly lower in our study group than healthy infants at both measurements.

**Conclusion:** There were no procedure-related complications. A smaller gain in FFM than expected was shown in this group of patients.
Acknowledgments

First, I would like to express my deepest gratitude to my supervisor Dr. Christopher Tomlinson for his immense support to my Master’s research and study, for his endless knowledge, patience, encouragement, and devotion in the past years. I could not have a better mentor for my Master’s research and I have been fortunate to have him as a supervisor. His academic instructions and guidance assisted me in writing this Master research thesis.

Beside my supervisor, my sincere appreciation goes to my co-supervisor Dr. Paul Pencharz for his guidance and insightful remarks. His suggestions helped me enormously in my Master research and is truly appreciated. It has been an honour working with him.

I would also like to thank my Committee member Dr. Jill Hamilton and my external examiner Dr. Deborah L. O’Connor for their precious time to evaluate my work in my Master research and for their valuable feedback.

Also, I would like to acknowledge my fellow Lab members Dr. Amr El-Shahed, Dr. Glenda Courtney-Martin, Mahroukh Rafii, Mary Ann Ryan, Abeer Almokbel, and Veronik Connan for their great help and efforts while conducting my Master research.

My further thanks go to the Clinical Research Center staff Dr. Karen Chapman and Johanne Fiest for assisting me during the time of body composition measurements. I am also grateful to Dietitians Joanna Benec and Kathryn Chambers who provided me with their helpful feedback and assistance.

Many thanks to the subjects who participated in this study and their families. This research could not have been possible without them. Their commitment and dedication is appreciated.

I thank The Saudi Scholarship Program, the Royal Embassy of Saudi Arabia in Canada, The Saudi Cultural Bureau in Canada, and King Abdulaziz University in Saudi Arabia for their financial and academic support.

I would like to give a special thank to my husband Dr. Hatem Sindi for his continuous support, his enthusiasm and his warm words of encouragement, and for always being there for me. I could not have finished my Master research without him.
Last but not the least, I am greatly thankful to my mother Dina Barakat, my father Abduljalil Bakhsh, and my family back home for always believing in me, for their unconditional love, prayers, support, and for sharing all my moments of happiness and sadness.
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Description of my Role in the Present Study

I was responsible for both the practical and the research parts of this study. First, I screened all patients admitted to the neonatal intensive care unit (NICU) at the Hospital for Sick Children who were diagnosed with gastroschisis for eligibility. I approached all parents of eligible subjects and explained to them the nature and the purpose of this study. I collected the signed informed consents for participated subjects. Second, I did all the data collection for this study either from the hospital’s software system and medical files or by personal interviews. I arranged for all the appointments for body composition measurements. Third, I was responsible for all the anthropometric and body composition measurements for all subjects. Fourth, I did all the statistical data analysis related to this study. Finally, I wrote and discussed the entire thesis for this project.
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AC</td>
<td>Abdominal Circumference</td>
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<tr>
<td>ADP</td>
<td>Air Displacement Plethysmography</td>
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<tr>
<td>BC</td>
<td>Body Composition</td>
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<tr>
<td>BF</td>
<td>Body Fat</td>
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<tr>
<td>BIA</td>
<td>Bioelectrical Impedance Analysis</td>
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<tr>
<td>BM</td>
<td>Body Mass</td>
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<tr>
<td>BMC</td>
<td>Bone Mineral Content</td>
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<tr>
<td>BMD</td>
<td>Bone Mineral Density</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BV</td>
<td>Body Volume</td>
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<tr>
<td>CA</td>
<td>Chemical Analysis</td>
</tr>
<tr>
<td>CCASS</td>
<td>Canadian Congenital Anomalies Surveillance System</td>
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<tr>
<td>CPU</td>
<td>Central Processing Unit</td>
</tr>
<tr>
<td>CRC</td>
<td>Clinical Research Center</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>Db</td>
<td>Body Density</td>
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<tr>
<td>DPA</td>
<td>Dual-Photon Absorptiometry</td>
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<tr>
<td>DXA</td>
<td>Dual-Energy X-ray Absorptiometry</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>ECW</td>
<td>Extracellular Water</td>
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<tr>
<td>EFW</td>
<td>Estimated Fetal Weight</td>
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<tr>
<td>FFB</td>
<td>Fat Free Body</td>
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<tr>
<td>FFM</td>
<td>Fat Free Mass</td>
</tr>
<tr>
<td>FM</td>
<td>Fat Mass</td>
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<tr>
<td>GA</td>
<td>Gestational Age</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal Tract</td>
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<td>GT</td>
<td>Gastrostomy Tube</td>
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<tr>
<td>HC</td>
<td>Head Circumference</td>
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<tr>
<td>HD</td>
<td>Hydrodensitometry</td>
</tr>
<tr>
<td>I</td>
<td>Electrical Current</td>
</tr>
<tr>
<td>ICW</td>
<td>Intracellular Water</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intrauterine Growth Restriction</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous line</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MUAC</td>
<td>Mid-Upper-Arm Circumference</td>
</tr>
<tr>
<td>NGT</td>
<td>Nasogastric Tube</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
</tr>
<tr>
<td>NMRI</td>
<td>Nuclear Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NPO</td>
<td>Nothing Per Oral</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>PICC</td>
<td>Peripherally Inserted Central Catheter</td>
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<td>PN</td>
<td>Parenteral Nutrition</td>
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<tr>
<td>PRU</td>
<td>Physiological Research Unit</td>
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<tr>
<td>QNMR</td>
<td>Quantitative Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>RV</td>
<td>Residual Lung Volume</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SEE</td>
<td>Standard Errors of Estimate</td>
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<tr>
<td>SPA</td>
<td>Single-Photon Absorptiometry</td>
</tr>
<tr>
<td>TBBM</td>
<td>Total Body Bone Mineral</td>
</tr>
<tr>
<td>TBW</td>
<td>Total Body Water</td>
</tr>
<tr>
<td>TDV</td>
<td>Total Daily Volume</td>
</tr>
<tr>
<td>TFI</td>
<td>Total Fluid Intake</td>
</tr>
<tr>
<td>TGV</td>
<td>Thoracic Gas Volume</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>UWW</td>
<td>Underwater Weighing</td>
</tr>
<tr>
<td>V</td>
<td>Voltage</td>
</tr>
<tr>
<td>VLBW</td>
<td>Very-Low-Birth-Weight</td>
</tr>
<tr>
<td>Z</td>
<td>Impedance</td>
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Chapter 1
Introduction

The period of infancy is characterized by rapid growth and changes in body composition (BC). Studies have shown a rapid fat deposition over the first six months of life followed by a more stable rate of fat gain during infancy \(^1,2\). Preterm infants in particular have shown to have a greater fat mass (FM), but diminished fat-free mass (FFM) when compared with term infants at term equivalent age \(^3-5\). They are often described as lighter and shorter than their term counterparts because of their affected BC and FFM-related linear growth.

Both nutritional and non-nutritional factors have been linked to these changes. Certain adaptive physiological mechanisms due to prematurity might trigger this rapid fat gain, including the hyperresponsiveness of pancreatic \(\beta\)-cell to glucose and the higher glucose utilization in adipose tissue \(^4\). Although this fat gain might protect the brains and nervous systems of these vulnerable infants from energy deprivation \(^6\), it might also lead to increased risk of metabolic syndrome, obesity, and neurocognitive outcomes later in life \(^7\).

To fully assess the growth and nutritional status of preterm infants, it is crucial to measure the BC and not just rely on standard anthropometry, as this will help in guiding nutritional therapy and determining possible causes of adult morbidity for these infants. Studies on preterm BC are scarce, however, and available data are from whole-body chemical analysis of stillborn preterm infants \(^8\). Although carcass analysis is considered the gold standard for measuring BC, it is inaccurate to compare the body constituents of a live preterm with a stillbirth. One reason for this is the water loss that occurs between death and the time of the analysis \(^9\).

BC assessment is recognized as the most accurate method of measuring infant growth and nutritional status. However, due to the challenges associated with the infant population, weight, length, and head circumference remain the routine clinical measurements \(^10\). Over the past several decades, various methods have been developed for the indirect assessment of BC in infants. Although some of these methods have technical limitations, they have the advantage of being noninvasive and applicable for longitudinal measurements in growing infants. Some of these methods include the total body electrical conductivity that has been used to estimate FFM, the dual-energy x-ray absorptiometry (DXA) method that has been proposed for the
determination of lean and fat body masses, and magnetic resonance imaging (MRI) for adipose tissue in neonates 11.

Air displacement plethysmography (ADP) is a relatively new method that has been used successfully to measure infants’ BC with very good precision 12. It uses the principle of densitometry, determining the body density by measuring the body mass and volume. From this, the percentages of FM and FFM are calculated. ADP has been validated in several studies of healthy infants 12–14. However, studies regarding this technique to measure BC of different groups of infants are ongoing.

In this study, we aim to analyze the BC and anthropometry of preterm infants with gastroschisis at the earliest point of stability both post-surgical closure and a month after the first measurement using the ADP technique. This will enable us to assess preterm infants’ growth and nutrition and the appropriateness of our current PN regimen. This study will also demonstrate the feasibility and utility of ADP in this high-risk population and generate interest in optimizing the growth of late preterm infants requiring surgery.
Chapter 2  
Background and Literature Review

2.1 Definition and Overview of Body Composition

The study of BC is a branch of human biology that examines the *in vivo* quantification of body components, the measurable relationships between components, and the changes in these components related to physiological or pathological conditions. Ranging from elements to tissues to organs, these elements are the building blocks that give mass, shape, and function to the body. In other words, BC is the accumulation of nutrients and other substances from the environment in the human body throughout a person’s lifespan.

According to Wang et al., the study of BC is organized into three areas: BC rules and models, BC methodology, and BC variation. The first area includes the components of the body and the links between them. The different components are categorized into various levels, as per the five-level model: atomic, molecular, cellular, tissue-organ, and the whole body as shown in Figure 1-1. In this model, the body mass is the sum of all the components at each level. The five-level model will be discussed in more detail in section 0. The second area of BC research involves the different methods available to measure the body components at the five different levels. The third area includes the changes that occur in BC due to physiological or pathological conditions such as growth, aging, race, nutrition, and some diseases.

2.2 History of Body Composition Assessment

In their review article “History of the Study of Human Body Composition,” Wang et al. speculate that studies of human BC began circa 440 BC. At that time, Hippocrates, the father of medicine, believed that the human body consisted of four elements: blood, phlegm, black bile, and yellow bile.

While non-experimental ideas on studying the human body as compartments started about 200 years ago, experimental studies began in 1843, when Schwann measured cadaver organs. At that time, cadaver autopsy was the only way to obtain quantitative data on BC. Then, in 1863, water content in adult human cadavers was studied by Bischoff. Thirteen years later, Fehling analyzed fetuses and infant cadavers for water content. Thereafter, water, fat, nitrogen, major minerals, and other chemical compositions of fetuses were assessed by Camerer and Soldner in 1900. A
whole-body assay for fetuses and infants was performed by Iob and Swanson in 1938. Two years later, Behnke et al. applied Archimedes’ principle of BC to estimate relative FM and FFM percentages in the human body.\(^{15}\)

The largest cadaver study that obtained significant adult BC data was the Brussels study in 1984.\(^{18}\) It is valuable to note that, until recently, cadaver autopsy was considered the gold standard method for measuring BC.\(^{19}\)

Clearly, advanced, non-invasive techniques used to measure BC originated long ago. Cadaver analysis eventually gave way to various and more advanced methods. After analyzing cadavers, researchers began to deepen their knowledge of BC by measuring body components such as urinary creatinine and body fluids, using indicator dilution methods, applying densitometric and radioactive techniques, and studying factors that might influence or change BC, such as age, nutrition, exercise, gender, race, and different diseases.\(^{15}\) In the early 20th century, scientists and investigators laid substantial groundwork in the field of BC study. In 1921, J. Matiegka reported an anthropometric model to estimate total body muscle mass.\(^{16}\) In the 1930s and 1940s, the field entered a golden era of many new philosophies and concepts, such as Behnke’s introduction of the underwater weighing method and two-compartment model, which offered an easy, simple, and practical way to measure FM and FFM in humans.\(^{20}\) In 1963, Brozek held the first BC symposium at the New York Academy of Sciences when a new reference body was established with a density of 1.064 and a fat content of 15.3% of the total body weight.\(^{21,22}\) These values are still used in some BC formulas. Brozek’s findings opened the door to the recent human BC research.

Special attention should be paid to a report published in 1992 by Wang et al. that proposed a new model. In this model, BC is divided into five different levels, with each level defining the components of total body mass. The five levels are atomic, molecular, cellular, tissue-system, and whole body, as shown in Figure 1-1. The main concept of this model is that higher BC levels are composed of lower-level components: “A classic example is that adipose tissue, a tissue-system-level component, includes components such as adipocytes at the cellular level, lipids at the molecular level, and carbon at the atomic level. Loss or gain of adipose tissue with a new intervention reflects changes in corresponding components at the cellular, molecular, and atomic levels.”\(^{23}\)
Figure 1-1: The Five Levels of BC

This comprehensive model helped to organize human BC research in several ways. First, it resolved the confusion in naming different body compartments, which was a major source of error in formulating equations. “For example, are lipid-free body mass, fat-free body mass, and lean body mass the same or different compartments?” Second, it defined each human BC compartment clearly. Third, it helped in the development of more complex BC equations.  

As shown in Figure 1-2, BC models range from simple to complex and are commonly used to describe BC at the molecular level. The simplest model, called the two-compartment (2-C) model, is widely used by physicians, researchers, and exercise physiologists. In this model, the weight is divided into FM and FFM. The more complicated three-compartment (3-C) model divides the weight into FM, lean mass, and bone. The most sophisticated model, the four-compartment (4-C) model, defines FFM as water, protein, and mineral or bone. Multicomponent models are recommended for use by researchers in order to obtain more accurate estimates of an individual’s BC.
Figure 1-2: BC Compartment

2.3 The Importance of Body Composition Measurements

Presently, most clinicians and researchers use body mass index (BMI: weight in kilograms divided by the square of height in meters) to identify overweight, obese, or underweight individuals, especially in large-scale studies. This method is widely used because it is simple, quick, effective, and applies to adult men and women as well as children. However, BMI alone does not consider the composition of the individual’s body; FM and FFM vary in BC for any given BMI, which means that people with the same BMI may have different FM and FFM levels. For example, a 180 cm-tall athlete weighing 90 kg may have the same BMI (27.7) as a sedentary person of the same height and weight, and both will be classed as overweight based on BMI calculations. Muscle is denser than fat and thus weighs more. Therefore, BMI might classify healthy active persons as fatter than they are. In addition, older people have more fat at any given BMI than younger people do. Therefore, it is recommended that researchers take BC measurements and not rely on weight or BMI measurements in classifying an individual’s fatness.

Measuring BC and knowing the percentages of body FM and FFM can help to predict future health and identify those at risk for diseases so that preventive intervention and management can take place. This also helps in formulating personalized dietary, exercise, and medicinal plans for
clients or patients; monitoring BC changes that occur when patients follow specific dietary, exercise, or pharmacological regimens; and assessing the effectiveness of these changes. Measuring BC aids the understanding of the effects of certain diseases and health conditions on energy metabolism and body components. This, in turn, leads to the development of more suitable therapies and to maintaining a healthy body weight loss or gain for patients and clients, especially for athletes such as bodybuilders, wrestlers, and powerlifters with minimal FM gain and FFM loss.

Measuring BC may help in identifying children who are at risk of obesity, thus preventing future health risks and diseases linked to excess body fat, such as coronary heart disease, high blood pressure, type 2 diabetes, metabolic syndrome, cancer, obesity hypo-ventilation syndrome, reproductive problems, and gallstones. The Heart and Stroke Foundation of Canada has reported an increase in cardiovascular diseases related to childhood obesity and indicates that the risk factors for cardiovascular diseases begin in early childhood. In keeping with international trends, accelerometer results from the 2007–2009 Canadian Health Measures Survey reveal that 26% of Canadian children and youth aged 6 to 19 years are overweight or obese. On the other hand, being underweight and having low fat levels poses health risks for children and adults. The body needs a certain amount of fat for normal physiological functions. Thus, too little body fat, as found in people with eating disorders, exercise addiction, and certain diseases, can lead to serious physiological dysfunction such as immune system abnormalities, reproductive system disorders, and central nervous system deterioration.

2.4 Techniques Used for Measuring Body Composition

Many techniques for assessing BC are available to researchers and clinicians. These include skinfold thickness, hydrodensitometry (HD), DXA, bioelectrical impedance analysis (BIA), ADP, MRI, and the stable isotope dilution method. However, regarding factors to consider when selecting a particular technique, Duren et al. comment, “There is no single universally recommended method for BC assessment, but each modality has benefits and drawbacks.” Limitations include lack of portability, lack of sensitivity, radiation exposure, requirement of the subject to be motionless, and high cost. Recognizing this, Garrow and Webster propose five factors that should be considered when defining a method as ideal for field studies: 1) initial cost; 2) training of the operator; 3) maintenance and operating costs; 4) precision; and 5) accuracy.
To better judge the validity of a new method in question, Lohman published a set of standards for estimating the magnitude of the standard errors of estimate (SEE) in young adult men and women that is applied by many researchers in the BC field. For fat percentage prediction errors, he used a 76.5-kg man and a 60-kg woman with fat percentages of 15% and 25%, respectively. The subjective rating he devised is as follows: a SEE of 2% is considered ideal, 2.5% is excellent, 3.0% is very good, 3.5% is good, 4.0% is fairly good, 4.5% is fair, and 5.0% is not recommended. From an application point of view, for a new method to be accepted as an accurate reference method, the SEE for fat percentage should be less than 3%. Errors between 3% and 4%, indicate limited validity, while errors exceeding 4% indicate too much variability.

This section addresses the most commonly used techniques for measuring BC. The definition, principles, basic assumptions, sources of measurement error, and validity in different groups are presented for each method.

2.4.1 Anthropometric Measurements

Anthropometry has been used for over a century to assess BC. It is defined as a set of noninvasive, quantitative, simple, and quick measurements that assess body size, structure, and composition. It may include measurements of weight, height, and body size, including circumferences (upper chest, chest, upper arm, waist, elbow, iliac crest, wrist, thigh, knee, calf, and ankle), skinfolds (cheek, chin, chest, biceps, thorax, umbilicus, forearm, supra-iliac, abdomen, thigh, knee, calf, suprascapular, subscapular, and triceps), and widths (shoulder, upper arm, elbow, and wrist). Tools used for these measurements include tape measures, stadiometers, weighing scales, skinfold calipers, anthropometers, segmeters, sliding calipers, and spreading calipers. Ideally, two people record the data. When measurements are repeated or are recorded more than once, the average or median value is used for data analysis. After the measurements are taken, the numbers are computed through equations using body density predictions and other proportionality estimates for data analysis.

Since my research is focused on the two-compartment model, I will discuss in detail methods that are directly related to that model.

Skinfold thickness, the thickness of subcutaneous adipose tissue, has been measured since the early 1900s. The skinfold technique directly measures the thickness of the skin and the
subcutaneous fat to represent subcutaneous fatness. Prediction equations are then used to estimate total body fat, including internal fat stores.

Some of the prediction equations for skinfold use generalized regression models. However, more than 100 population-specific equations are available in the literature to predict body density from anthropometric measurements and, subsequently, percentage body fat. These equations are based on certain assumptions that might be a source of substantial error, including overlooking the differences in skinfold compressibility between body sites, gender, age, and population; individual fat distribution patterns when predicting total body fat; the non-linearity in the relationship between subcutaneous FM and total body FM; and the variability of FFM (water, protein, bone mineral, and non-bone mineral) proportions among individuals.

Other potential technical and biological errors for the anthropometric measurements technique include:

1) Failing to choose the appropriate technique for taking the measurement
2) Failing to calibrate the instrument or caliper before using it
3) Failing to use the same type of instrument for subsequent measurements (the use of different caliper types has contributed to errors in the measurement of subcutaneous fat)
4) Failing to locate the correct site for the measurement.
5) Failing to grasp the skin and the subcutaneous tissue without also grabbing the underlying muscle tissue
6) Failing to choose the right time and state for taking the measurement (for example, it is not recommended to take a skinfold thickness measurement right after training, sauna, or showering because of the effect of hyperemia that might cause a falsely increased measurement)
7) Failing to take the mean or the median as the measurement, which could lead to related random errors (the usual practice for measuring skinfolds or girths is to take multiple readings and then calculate their mean or median)
The precision and accuracy of the skinfold method have been shown to be both highly variable and operator dependent when assessing an individual’s body FM. Skinfold thickness is accepted as a body fatness predictor because subcutaneous fat (40–60% of total body fat) can be directly measured with a caliper. However, this method can only reflect subcutaneous fat and cannot be used to reliably measure internal or visceral fat. Its accuracy is affected when no standardized methodology is used, the knowledge of general assumptions to understand its methodological errors is limited, and the equation selected to predict body FM is inaccurate \(^{39,40}\).

In adults, skinfold thickness has been shown to be as valid as any other method for the measurement of absolute FM and FFM. It also is valid in situations where there are changes in FM and FFM, even in populations where the composition of FFM is quite variable, as in the elderly \(^{41}\).

There is insufficient evidence regarding the validity of the skinfold thickness technique in children, especially in prepubertal children. In children and adolescents, skinfold thickness equations used to predict body fatness are generally derived from samples of healthy individuals. Therefore, the researcher or clinician might use an equation that is not applicable to the population under study \(^{42,43}\). Moreover, concerns about age- and disease-related variability in the FFM composition and the skinfold compressibility affect the validity of the technique in this age group \(^{44,45}\). As Forbes showed in his article on body composition in children how the ratio of extracellular fluid volume to intracellular fluid volume is higher during infancy and falls progressively during childhood, until it reaches to its lowest point in early adulthood \(^{46}\). It is also has been shown that some disorders like malnutrition, muscle dystrophy, renal failure, and growth disorders have a negative effect on the FFM \(^{45}\). In a group of chronic renal failure patients the validity of skinfold thickness was studied against DXA, and showed significant variation between methods \(^{47}\).

However, there are some studies that discuss skinfold thickness validity in children. Reilly et al. studied the commonly used equations for body fat predictions from skinfold thickness in healthy prepubertal children by comparing them to measured fatness values from HD \(^{48}\). They confirmed that there was a poor agreement between fat estimates from the reference method used and measurements from skinfold thickness. They also suggested that caution should be taken in predicting body fatness from skinfolds in children. In a study by Loftin et al., anthropometry and
skinfold values were compared to values from DXA. Anthropometry and skinfold were found to underestimate DXA-measured fat percentage and to overestimate FFM 49.

It may be difficult to perform an accurate measurement in the very young, but reliable measurements are possible with sufficient training. Numerous prediction equations are available to relate anthropometrics and skinfolds to measured FM for infants. Examples of these equations include those by Dauncery et al. in 1977, Catalano et al. in 1995, and Lingwood et al. in 2012 50,51.

Despite their significant issues, anthropometric measurements are noninvasive, inexpensive, quick, and easy to obtain. They require minimal training, are portable, can be performed at the bedside of patients or immobile subjects, and are suitable for large field studies. Additionally, measurements are easy to obtain in most age groups, including infants 52. As a result, they are still the most widely used method 34.

2.4.2 Hydrodensitometry (HD)

HD or underwater weighing (UWW) estimates total body volume from the water displaced by the subject’s body after it is fully submerged. HD is based on Archimedes’ principle that states the volume of displaced fluid is equivalent to the volume of the object fully immersed in that fluid. In other words, the weight of the displaced portion of the fluid is equivalent to the magnitude of the buoyant force acting on the subject. Archimedes’ principle is applied here by comparing the mass of a subject in air and underwater.

Since it is impractical to use the old approach of directly measuring the volume of displaced water using a burette located at the side of the volumeter, UWW mostly employs scales to calculate the weight loss of the subject underwater. This weight loss is directly proportional to the volume and weight of the water displaced by the body volume 53. After the body weight and volume are measured, body density (Db) is calculated by dividing mass (BM) by volume (BV), i.e. \( Db = \frac{BM}{BV} \). To accurately estimate Db, BV must be corrected for residual lung volume (RV), usually 1–2 L, and for gastrointestinal tract (GI) gas volume, around 100ml. GI gas volume is small and is not measured, but RV is significant and can be measured by using either the closed-circuit approach (oxygen, nitrogen, or helium dilutions) or the open-circuit approach (nitrogen washout). These techniques yield precise estimates of RV and can be done either on
land or when the subject is under the water for the procedure. However, measuring RV underwater provides a more accurate estimate of Db. Consequently, using the Db calculated previously, %BF could be estimated using 2-C or multi-compartment BC models. HD is often considered the standard when compared to other methods, and the gold standard by some researchers, when it comes to measuring BV and Db. However, that does not make it error free. According to Behnke et al., RV is the major source of error that affects the estimates of Db and %BF in HD. Other sources of error include body weight, underwater weight, and water temperature, which accounts only for 0.0006g/cc. When the error from RV is added, the total technical error of Db measured by HD is 0.0015 g/cc, which is equivalent to 0.7%BF.

It is also valuable to note that numerous researchers have shown that the error in HD increases when the 2-C model conversion formulas are used instead of multi-compartment model conversion formulas to estimate %BF, where the densities of the composition of FFM are assumed to be constant for all individuals. In fact, density varies with age, gender, ethnicity, health conditions, and activity levels. Therefore, it is recommended to use population-specific conversion formulas that are reported in the literature when the 2-C model is used or to use a multi-compartment model when possible.

Other, subject-related limitations for HD might lead to error in measurement. When an autopsy scale is used to measure the weight of the subject underwater, a larger error may occur because of inaccurate weight detection, owing to the subject’s inability to stay motionless. In addition, some subjects, particularly children, the elderly, or sick people, find it difficult to accurately perform the maximal exhalation maneuver underwater. This maneuver is necessary for measuring RV. HD is also highly reliant upon subject performance; this is particularly problematic in children and obese subjects because it is difficult for them to submerge completely. It also is unsuitable for infants, is expensive, is time consuming, and requires a skilled technician to perform it accurately.

It is difficult to determine the validity of HD because it is often the benchmark to which other methods are compared. Nevertheless, based on the available literature, HD is generally accepted as a valid method for measuring BV and Db, and it is considered to be fairly accurate when corrected for the aforementioned sources of errors.
As mentioned, HD administration has proven to be difficult, particularly for children. Multiple tests of maximal exhalation and complete head submersion are required in order to perform a successful HD test. This fallibility of the HD method tends to increase in younger children, particularly among those aged 7 and under, as it is noticed from the literature that most of the subjects who participated in studies using HD are over 7 years old. The source of error in this group of subjects is derived not just from measuring the lung volume itself, but also from the discomfort and perhaps even fear of children when submerged, especially in very young ones. Some researchers have introduced creative technical ideas in order to alleviate the problem of submersion when the subject’s lung volume is at RV. For instance, C. Grieve and M. Henneberge attempted to use a snorkel to aid in underwater breathing for children aged 5.4 to 12.1 years. The study concluded that the use of a snorkel allowed the BC assessment of younger children to be more comfortable and enjoyable when submerged.

2.4.3 Dual-energy X-ray Absorptiometry (DXA)

Before the use of DXA, several techniques were developed to measure bone content and BC using the same concept. In the early 1960s, single-photon absorptiometry (SPA) was used to determine the mineral content of bone, where iodine-125 was used as the photon source. In the 1980s, dual-photon absorptiometry (DPA) was used to assess total body bone mineral (TBBM) and bone mineral density (BMD) using gadolinium-153 as the photon source. Developed in the 1990s, dual-energy x-ray absorptiometry uses an x-ray tube instead of radionuclide sources to convert the polychromatic x-ray beam into low- and high-energy peaks. The DXA machine comprises a computer system, a scanning table, a detector, and x-ray sources. It sends the x-ray peaks through the bone and other tissues being tested. The denser the tissue, the fewer x-rays transmit through to the detector. The number of x-rays that penetrate the bone from each of the two x-ray sources is measured by the detector. This information is then used to calculate the average density of the bone. This improved technique provides greater precision and accuracy in measuring BMD and soft tissue composition (FM and FFM) when compared to SPA and DPA.

Importantly, there are three different manufacturers of DXA scanners: Hologic, Lunar, and Norland. Although they are all based on the same principle and physics, each manufacturer has developed different models and software, which in turn leads to variations in body composition results. For example, in a study by Economos et al. that compared different DXA devices to in
vitro chemical analyses of a femur from a cadaver, the Lunar scanner showed higher values of bone mineral content (BMC), but lower values were obtained from the Hologic and Norland scanners when compared to values from the chemical analysis\textsuperscript{65}. This might be a source of the variability in results reported in DXA validation studies. In order to eliminate this source of error, it is recommended that the same device and software be used in longitudinal or cross-sectional assessments and studies. Finally, not all software has normative data for all groups and cannot calculate Z-scores.

Other sources of measurement error for DXA include large clients whose body length or width exceeds the size of the scanning bed; subjects who weigh more than 100 kg, as the accuracy of body composition estimates depends on subject thickness; and inappropriate positioning of subjects on the scanning bed. The machine is also expensive and is not readily available. On the other hand, the DXA technique is preferable in certain situations over other techniques because it can be used in all age groups, requires no food or fluid restrictions before the test, is minimally affected by normal fluctuations in FFM hydration \textsuperscript{66}, needs minimal subject compliance and technician skill, and provides regional body composition assessment in addition to whole-body FM, fat free-mineral free masses, and bone mineralization \textsuperscript{67}. It is also still the preferred method when the target outcome is bone measurement \textsuperscript{68}. Nevertheless, like other techniques, DXA relies on certain assumptions. It is assumed that the amount of fat in bony regions is the same as the amount of fat in bone-free regions, that the regional fat distribution is the same among populations \textsuperscript{69}, that the measurements are not affected by the thickness of the body \textsuperscript{70}, and that hydration of the FFM is constant \textsuperscript{66}.

It is essential to have a SEE value between 2\% and 3\% and a systematic bias of less than 2\% between criterion and DXA methods to decide DXA’s accuracy \textsuperscript{71}. In the literature, when DXA was compared to multicomponent model estimates of %BF, some researchers reported that the predictive accuracy of DXA was better than that of HD \textsuperscript{72,73,74,75}. On the other hand, other studies have shown that HD is more accurate than DXA \textsuperscript{76,77}. In a summary of DXA validation studies by Lohman and colleagues, it was concluded that DXA and multicomponent models are in agreement in terms of mean values. In general, DXA estimates of % BF were within 1\% to 3\% of multicomponent model estimates \textsuperscript{78}. Additionally, when Wang et al. compared DXA to a six-compartment chemical model of FM, they reported a 1.7 kg FM SEE for DXA \textsuperscript{56}. Significant attention has been paid to studying the validity and reliability of DXA for BC assessment in
adults and children, but that is not the case when it comes to infants and children younger than 2 years of age. The scarcity of studies in this population is probably due to concerns about ionizing radiation exposure. However, researchers have studied the amount of radiation exposure from DXA scans and found that the radiation dose associated with the x-ray exposure is low—less than a weekly exposure of environmental background radiation—and that it is a safe procedure for adults and infants 79, 80. The available studies testing the validity of DXA in infants were performed either on piglets, phantoms, or human infants and were compared predominantly to direct piglet carcass analysis. Of the three studies that have tested the validity of DXA using carcass analysis, the one by Koo et al. showed a higher mean FM in piglets than the direct carcass analysis 44. Differences in manufacturers, hardware, and software algorithms between DXA machines may affect lean mass and FM estimates with greater errors in smaller infants 44. Other sources of error for infants include the effect of the use of blankets plus diapers, and the effect of movement during a DXA test. Both have shown to affect results, but not the use of blankets alone 81. In order to maintain body temperature and prevent excessive movement in the infant, Koo et al. suggested that the infant can be swaddled, but the same size and type of blanket should be used for all scans 82. It is valuable to note that the DXA tool is a useful technology to use for infants because it is able to estimate regional adipose tissue and to analyze FFM in terms of lean mass and bone.

In the pediatric population, it is common for researchers to use DXA as a reference technique rather than other BC techniques 83–85. Researchers such as Lapillonne et al. and Shypailo et al. have questioned this approach, however, and have concluded that DXA cannot yet be considered the gold standard method for comparison in this population 86,87. Moreover, not all DXA software has normative data for very young children.

2.4.4 Bioelectrical Impedance Analysis (BIA)

In the early 1960s, Thomasset and colleagues established the basic principles behind BIA 88. They first described the proportion of extracellular water in total body water (TBW) by using measures of impedance at low and high frequencies 89. Then, in 1969, Hoffer et al. reported an association between total body impedance measures and TBW 90. From that point, BIA began to be used as a tool for assessing TBW and analyzing BC, and the first commercial impedance analyzer became available in the mid-1980s. Being a quick, noninvasive, and inexpensive
technique, BIA does not require technician skill, maintains client privacy, and can be used easily on obese individuals. BIA instruments introduce a known amount of a low-level electrical current (I), about 500–800 A, most often at a frequency of 50 kHz, into the body. The current passes between two electrodes, the source and detector, which are usually located on the wrist and the ankle. The current generates voltages between different points in the body following Ohm's law, and flows through conducting materials found within the body between the electrodes. Water and intracellular and extracellular fluids in the human body are excellent electrical conductors because of the electrolytes present in them, unlike other tissues that are low in water content (e.g., fat, which is a poor electrical conductor). The current flows mainly through the water found in the body; at low frequencies (1 kHz), the current passes through extracellular water (ECW) only, but at higher frequencies (500–800 kHz), it passes through cell membranes and intracellular water (ICW) \(^91\). TBW can thus be estimated from the impedance measurement, where impedance (Z) is the ratio of the voltage (V) produced between the two electrodes and the current (I). After TBW is estimated, FFM can be predicted since the water content of the fat-free body is relatively large (73% water) \(^92\). Several BIA prediction equations have been developed for TBW, FFM, and % BF.

However, like all BC methods, BIA depends on certain assumptions. The major assumption here is that the human body is shaped like a perfect cylinder with a uniform length and cross-sectional area. Of course, the body has a complex geometric shape and is better illustrated as five cylinders (two arms, two legs, and a trunk) than as one large cylinder. It is also assumed (incorrectly) that the specific resistivity of the body’s tissues is constant, even differing between body segments, because of the variation in tissue composition, hydration, and electrolyte concentration \(^93\). Moreover, the user of BIA should be aware of the sources of measurement error to be avoided when possible. These include the use of different types of BIA analyzers interchangeably, as studies have shown that different instruments give different body resistance values when used on the same person \(^94,95\), factors that alter the individual’s hydration, such as eating, drinking, dehydrating, and exercising, as such factors have been shown to affect the total body resistance and, therefore, estimates of FFM when measured by BIA \(^96,97\); changes in body position, which may cause alterations in the Z values because of fluid shift \(^98\); and room temperature, which may affect skin temperature and, therefore, the resistance values. A study conducted by Caton et al.
shows that cool temperatures decrease skin temperature, which leads to an increase in total body resistance value and a drop in estimated FFM.

Most of the prediction equations published for BIA use a two-compartment model originated from densitometry, TBW, or DXA as the criterion measure. Such equations are only as accurate as the criterion method used for the equation selected. In addition, most of these equations are of limited general use because of a narrow age range and specificity to the racial and ethnic makeup of their sample. The majority of them were designed for Caucasians only. Errors of prediction will be exacerbated for special groups such as clinical cases or obese people.

The literature has shown conflicting data on the validity of the BIA method and its estimates of BC. A major factor affecting impedance measurements is the disproportionality of the body size, shape, and composition between limbs and trunk. In obese subjects, the measurements will be more affected because of their greater proportion of body mass and body water in the trunk, their greater hydration of FFM in general, and their greater ratio of ECW to ICW. In athletes and some clinical conditions where water balance is disturbed, bioimpedance and TBW assumptions will be altered significantly and thus considered invalid. However, BIA is still a valuable tool to assess nutritional status in cancer and HIV patients.

In patients with protein calorie malnutrition, the balance of ICW is disturbed. As a result, bioelectrical impedance does not appear to be useful in assessing the response to parenteral and enteral nutrition in terms of changes in FFM that reflect protein accretion. In addition, changes do not appear to be accurately and reliably identified by BIA in the obese who are experiencing acute weight changes due to dieting and in those who are experiencing acute weight loss due to protein calorie malnutrition. According to the literature available, BIA has the ability to estimate BC at a point in time, but its ability to track changes over time is questionable.

It has been shown that BIA underestimates FM in extremely obese adults. Similarly, this underestimation of FM was shown in studies of obese children and adolescents when BIA was compared with DXA. In children, it has been seen that BIA might serve as a valid tool to estimate BC at the group level but not at the individual level, especially when the device has been used widely in clinical and field settings due to being relatively small, portable, and cheap compared to other sophisticated methods.
The prediction equations used to estimate BC for infants are based on certain assumptions, such as constant tissue hydration\textsuperscript{93,121}. As infancy is a period of rapid fluid fluctuations where fluid distribution and electrolyte concentrations between ECW and ICW are affected, BC estimates using BIA are considered inaccurate and unreliable, especially at the individual level\textsuperscript{122,123}.

### 2.4.5 Magnetic Resonance Imaging (MRI)

The MRI technique was first called zeugmatography, and later nuclear magnetic resonance imaging (NMRI). However, the negative associations with the word “nuclear” in the late 1970s led to the exclusion of this word, and thus NMRI became MRI. Unlike computed tomography (CT) scans, MRI does not use ionizing radiation; instead, a computer-generated image is created from radio frequency signals emitted by the interaction between hydrogen nuclei (protons). Hydrogen nuclei behave like tiny magnets. When a subject is placed inside an MRI magnet, the hydrogen protons line themselves up and a radio frequency field is applied to the body tissues in order to get hydrogen protons to absorb energy. When the radio wave is turned off, the protons return to their original sites and release energy that is absorbed in the form of radio signals and used to generate the image. MRI is considered an accurate method for measuring BC. It provides high resolution and quality imaging for BC, separates total adipose tissue into its subcutaneous and visceral components, allows the acquisition of slices and volumes of the body with any orientation without changing the position of the subject, and takes a reasonable amount of time to obtain an image (less than 30 minutes for a whole-body scan)\textsuperscript{124}. This is unlike the amount of time shown in earlier studies. For example, a set of abdominal MRI images used to take between 8 and 16 minutes\textsuperscript{125,126}. Now, the same image can be taken within just 25 seconds\textsuperscript{127}. However, the subject must stay motionless during the test, and its use is limited due to high costs, limited availability, and a tendency to be more time consuming than other BC assessment techniques\textsuperscript{31}.

MRI is considered a reference method for total and regional BC assessment. Several studies available in the literature support the validity and accuracy of MRI in estimating adipose tissue and skeletal muscle by comparing it with human cadaver analysis. In 1994, Abate et al. compared MRI measurement of abdominal subcutaneous and visceral fat to measurements from the same abdominal fat compartments from three human cadavers. The difference between the two methods was about 6\%\textsuperscript{128}. Engstrom et al. (in 1991) and Mitsiopoulos et al. (in 1998) performed a similar analysis, comparing cross-sectional area measurements of different body
parts of skeletal muscle in cadavers using MRI. Both reported a very strong correlation between the two methods \(^{129,130}\).

MRI does not involve radiation exposure, which makes it a good technique for use in infants and children. MRI has been shown to be a feasible and highly precise BC assessment method for the infant population, especially for total body adipose tissue. Harrington et al. studied adipose tissue volume and provided MRI estimates that approximate the total body FM of the reference infant. They showed that the interobserver CV\% was 2.4\% for subcutaneous adipose tissue and 17\% for internal (non-subcutaneous, including visceral) \(^{131}\). Another study by Olhager et al. found the same agreement between MRI total body adipose tissue volume estimates and the values from the reference infant, with high precision for total and subcutaneous adipose tissue, but lower precision for visceral adipose tissue. This lower precision for visceral adipose tissue is probably due to the very small visceral adiposity in infants \(^{132}\).

There are, however, several factors that might affect MRI’s accuracy in infants. Since body movement during a test creates artifacts, it is recommended that the scan be done when the baby is sleeping or after s/he has been fed. It is more difficult to keep older infants still during a scan, so MRI will be feasible only in infants less than 6 months of age \(^{133}\). The main limitation for the use of MRI in children is that the child should stay in the scanner-enclosed tube for a certain amount of time, which can be especially difficult for young children \(^{134}\).

2.4.6 Stable Isotope Dilution

Water is the largest single component of the body, typically accounting for over 60\% of the body’s weight, approximately 73\% of its FFM, and 27\% of its solids \(^{135}\). However, these percentages can vary with age, level of fatness, and health status. For example, it may account for 40\% of the body weight in obese adults \(^{136}\). First recommended by Pace and Rathbun in 1945, measuring TBW can be helpful in estimating both FM and FFM, assuming a constant hydration value of 73\% \(^{137}\). In this method, a known amount of an isotopically labeled tracer (deuterium or oxygen-18 labeled water) is administered into the body. Before the administration of the tracer, a fluid sample is collected from blood, saliva, or urine to provide a baseline measure. A second sample taken approximately 2–3 hours after the administration provides a measure of the concentration of the tracer after it equilibrates with the water in the body. From this, TBW can be measured and FM and FFM can be estimated based on four basic assumptions \(^{138}\): First, the
tracer is distributed only in body water, although it is known that tracers exchange with non-aqueous molecules to a small degree \(^{139}\). Second, the tracer is equally distributed in all water compartments; differences in molecular weight between the isotopic tracer and body water can lead to a change in the abundance of isotopes in the product relative to the reactant when it undergoes physical or chemical change \(^{140}\). Third, the rate of the tracer’s equilibration is rapid; it has been shown that tracer equilibration occurs three hours after the tracer is administered, but a small amount of equilibration may continue over the next hour. Thus, four hours is the recommended time, especially for pregnant women or people with edema \(^{139}\). Fourth, neither the tracer nor body water undergoes metabolism during the process of tracer equilibration; body water is in a constant state of flux, including inputs from beverages, water in food, oxidation of fuel, and outputs of urine, insensible losses, and stool \(^{141}\). For the test, the subject should fast overnight with no fluid intake, avoid exercising after the last meal, and avoid taking anything by mouth during the sample collection period.

It is generally agreed that the accuracy of the isotope dilution method is excellent for measuring TBW \(^{139,142}\). The accuracy of this method depends on the uncertainty in estimating the amount of tracer that exchanges with the non-aqueous compartments, approximated at about 1%. It also depends on the uncertainty in estimating FFM due to the assumption that the hydration fraction of the fat free body (FFB) is constant, at about 73%. This value is fairly stable among adults \(^{142}\). However, biological variability in the water content of the FFB corresponds to a 3.6% error in body fat (BF) \(^{78}\). Therefore, in certain groups, such as children and people with edema who have higher water content than regular adults, this method should not be used singularly for the estimation of BC, and those constants used in adult BC methodology should not be used in pediatrics. The use of these values in children will substantially overestimate the fatness of children, so it is recommended to use age- and sex-specific constants for the composition of FFM \(^{143}\).

Several factors may make employing the isotope dilution method challenging in infants. Dose spillage is a common problem, but using a syringe can minimize that. The equilibration period is a time-consuming process. There is also difficulty in dosing and collecting serial samples from infants; fresh cotton balls are needed for each data point. The hydration of the FFM in this group is unstable, though FFM hydration reference values could be used by month of age to adjust for
this. Despite these challenges, the isotope dilution method directly estimates the most variable component of infant FFM and can be used from birth\textsuperscript{144--146}.

2.4.7 Air Displacement Plethysmography (ADP)

Early attempts at using ADP to assess BC began in 1963, when Gnaedinger and other researchers tried to determine human Db using ADP. Unfortunately, such attempts were unsuccessful due to the technical difficulties associated with temperature, pressure, and relative humidity regulations\textsuperscript{147}. In 1995, however, Dempster and Aitkens devised a new system, known as the BOD POD\textsuperscript{©}, that overcame some of the limitations of past ADP techniques through improved precision and accuracy\textsuperscript{148}. ADP has thus been a viable system used for routine measurements of human BC since the mid-1990s\textsuperscript{149}. Two devices for ADP are available commercially: the BOD POD\textsuperscript{©} (for adults and children over 6 years of age) and the PEA POD\textsuperscript{©} (for infants up to 8 kg). A toddler seat can be placed in the BOD POD\textsuperscript{©}, making it feasible for measuring toddlers from age 2\textsuperscript{150}. ADP offers several advantages over established reference methods. It is quick, comfortable, automated, noninvasive, requires exposure to neither water nor radiation, and has no strict restrictions regarding movement. ADP is a safe measurement process that accommodates various subject types (e.g., children, obese, elderly, and disabled persons)\textsuperscript{149}. It is not yet fully evaluated or accepted because of its novelty. Therefore, it is important to establish its validity, reliability, and practicality in various populations.

ADP uses the relationship between pressure and volume in addition to the control for changes in temperature and gas pressure when the human body is positioned in an enclosed chamber. Body volume (BV) is determined by measuring the changes in pressure within the enclosed chamber. Boyle’s Law describes the pressure-volume relationship under isothermal conditions, where the temperature of air remains constant as its volume changes. The air present in the lungs and on the surface of the body (skin, hair, and clothing) acts isothermally. However, most of the air in the enclosed chamber acts adiabatically, which means that the air temperature does not remain constant as its volume changes and the air in the chambers compresses and expands (i.e., it freely gains and loses heat during compression and expansion). This relationship between pressure and volume of air under adiabatic conditions is defined by Poisson’s law\textsuperscript{149}. Thus, the software in both the BOD POD\textsuperscript{©} and the PEA POD\textsuperscript{©} uses Poisson’s law. However, after the BV is estimated
using Poisson’s law, the actual BV of the subject is determined by accounting for the isothermal effect of the body’s surface and the gas in the lungs.

The BOD POD© is an air displacement plethysmograph that uses whole-body densitometry to determine BC based on modeling the body into two compartments—a fat compartment and an FFM compartment (protein, water, mineral, and glycogen). It measures body mass (weight) using an electronic scale that is integrated within the system, and volume with the subject sitting inside the BOD POD© chamber. Once the subject’s mass and volume are measured, Db can be calculated as follows: Density = Mass/Volume. The relative proportions of body fat and lean body mass are then calculated from the Db using specific densitometric equations. In essence, ADP follows the same concept as HD, but air is used instead of water to measure BV based on the physical relationship between pressure and volume. This relationship allows for the derivation of an unknown volume by directly measuring pressure.

The BOD POD© system consists of two chambers: a front (test) chamber where the subject sits during a test and a rear (reference) chamber. A molded fiberglass seat forms a common wall between the two chambers. A moving diaphragm mounted on this common wall is oscillated during testing by computer control. The oscillating diaphragm creates small volume changes between the two chambers. When the volume is increased in one of the chambers, it is decreased by the same amount in the other chamber, and vice versa. This produces small pressure fluctuations. During a test, the interior volume of the empty chamber is determined first, and then the volume is determined when the subject is seated inside the chamber. When the subject sits inside the chamber, a volume of air equal to his/her body volume is displaced. Thus, BV is calculated simply as the difference between the chamber volume when it is empty and when the subject is inside the chamber. This provides an estimate for a raw body volume value. To obtain an accurate BV value, it is necessary to account for the effect of clothing, hair, skin surface area, and lung volume. Compressing hair with a swim cap and wearing minimal, tight-fitting clothing (a bathing suit, for example) can solve the problem of skin and hair, however. The isothermal effect related to skin surface area is minimized by estimating total body surface area using the formula of Dubois, and the area artifact is automatically accounted for by the BOD POD© software. The thoracic gas volume in the lungs is accounted for by two means, either by using an estimated value based on standard prediction equations or by measuring it directly through a hose that is connected to the subject. It is highly recommended to measure
thoracic gas volume (TGV) without using estimated values, especially in research and clinical use. When measuring TGV, the subject breathes normally through the breathing hose, unlike in underwater weighing, which requires a difficult maximal exhalation maneuver. The airway is occluded at mid-exhalation while the subject uses normal tidal breathing. At this point, the subject puffs gently against the closed airway (performing alternating contraction and relaxation of the diaphragm). This creates a small change in the pressure between the lungs and the external volume that will be used to measure TGV. The BOD POD© software uses the following equation to determine BV: \( BV \text{(L)} = BV \text{ raw} - (\text{surface area artifact} + 40\% \text{ TGV}) \).

As is shown in this chapter, many methods and techniques are available for measuring BC in different ages and groups. Each method has its advantages and disadvantages, and some could be used in a specific life stage or group but not another. In my study, I will use the ADP technique, specifically the PEA POD© device for infants. More details about the PEA POD© will be provided in the methodology chapter. In the following paragraphs, I will present a detailed discussion of the use of the ADP technique in clinical studies.

2.4.7.1 Clinical Studies Using Air Displacement Plethysmography

2.4.7.1.1 Studies in Adults

In the mid-1990s, the BOD POD© became the first commercially available ADP device. Around 1,300 studies have been conducted to validate the reliability and suitability of using the BOD POD© to assess BC in adults. First evaluated by Dempster and Aitkens using objects ranging from 25 L to 150 L in volume (the general range of the human body’s volume), it showed a mean error of less than 0.1%, except for the smallest volume (25 L), where it was 0.13%. McCrory and his team were the first to evaluate it using humans. They found an excellent validity of the BOD POD© compared to HD, with a difference of only 0.3% in BF estimates between the two methods. Since then, several researchers have conducted studies to test the accuracy of the BOD POD©. Some reported small differences in average Db measured by the BOD POD© and HD in adults (≤ 0.002 g/cc), while others reported greater differences (0.003–0.007 g/cc). Most of the ADP validation studies compared the BOD POD© to HD and/or DXA in terms of %BF estimates. Most studies that used HD as the criterion method employed young to middle-aged adults as the subjects, except for a study by Nunez and colleagues that included subjects up to 86 years of age. In a review article of 15 studies of
adults, Fields et al. reported average differences in %BF between ADP, HD, and DXA, ranging from −4.0% to 1.9%, with SEEs from 1.8% to 3.7%BF. All SEE values above 3% were obtained from only three studies that compared the BOD POD© to DXA 149. According to Lohman, these SEE values (≤ 3%) are considered in the acceptable range 33, while the largest differences in %BF (−4.0% and −3.3%) were obtained from the two studies with the smallest sample sizes (n ≤ 10) 159,163. Moreover, some researchers found that gender may have a significant effect on %BF, with an underestimation in men and an overestimation in women between ADP and HD 164,165. On the other hand, others found that gender had little or no effect on %BF 153,162. In the studies that reported significant differences between the methods, ethnicity was mixed, but its effects were not examined in those studies 157,160. In other studies involving mixed ethnicity, however, ethnicity did not contribute significantly to differences between the methods 153,162.

Some researchers have also studied the accuracy of ADP against multicomponent models. Fields and colleagues concluded that the accuracy of the BOD POD© and HD were similar when each method was evaluated against 4-C models in adult females 154.

In a more recent study performed on 24 adults in 2007, Anderson concluded that the BOD POD© is highly reliable in estimating body fat taken on the same day, but it shows significant differences in estimating body fat taken on different days 166.

Other researchers have focused on studying factors that influence the estimation of body volume in the BOD POD©, including the effects of clothing, moisture, metabolism, and the use of predicted or measured lung volumes. As mentioned, excess clothing results in underestimation of body volume and, consequently, an underestimation in fat percentage because of the increased isothermal air trapped between clothing layers. Fields et al. showed no difference in %BF between women who wore a one-piece or two-piece swimsuit. On the other hand, when a hospital gown was worn, %BF was lower by 5% 167. In another study by Fields et al., the effect of moisture on body volume was studied on the body, hair, and the swimsuit. They found that moisture can change the compressibility of air next to the body surface in addition to falsely increasing body weight, which leads to %BF underestimation 149. When the subject is recovering from a situation that elevates metabolism (for instance, exercise), his/her breathing pattern will fluctuate, which can confound estimation of thoracic gas volume. In the BOD POD© system, it is assumed that breathing patterns are similar during raw body volume and thoracic gas volume
measurement, which is not the case when the subject is recovering from physical or thermal stress. In a preliminary study by Fields and Hunter, unpublished observations showed that BF measured using the BOD POD© was 2.3% lower when measured 10 minutes after HD than when it was measured before HD. It is usually recommended to use measured lung volume rather than predicted lung volume to minimize sources of error. However, whereas some researchers reported that there was no significant difference between mean predicted and measured thoracic gas volumes, others reported that predicted thoracic gas volumes were higher than measured thoracic gas volumes using the BOD POD©.

2.4.7.1.2 Studies in Children

ADP is preferred over HD and other BC assessment methods for use in children. This is due to its ease of use, subject compliance, lack of radiation exposure, and noninvasive nature, especially for younger and sick children. The number of studies evaluating ADP in children is very limited; most have yielded results similar to those in adults in terms of validity.

In 2005, Fields et al. published a review article on ADP’s validity and precision. The article points out that until then, only six studies had compared ADP and HD in measuring %BF in children. Four of the studies concluded that there was no significant difference between the two methods, while one study showed higher %BF using ADP. The last study resulted in opposite findings with a lower %BF with ADP. However, it was suggested that laboratory- and/or technical-related errors are responsible for the differences between methods. For example, a possible confounding variable may be the measurement of lung volume. In observing the use of HD in children, some studies obtained residual lung volume on land while others obtained it during submersion in water. For ADP, the predicted TGV estimates have been used in some children rather than measured TGV. In addition, knowing that the ratio will be higher in children than in adults, some researchers argue about the effect of the ratio of chamber volume to subject volume on optimizing the precision of body volume measurements when using the BOD POD©. Gnaedinger et al. and Petty et al. suggest that a smaller ratio of chamber volume to subject volume would increase the precision of body volume measurements, which would, in turn, improve results. However, the mean ratio of chamber volume to subject volume was calculated from data obtained by Dewit et al., assuming a BOD POD© chamber volume of 450 L to be 14:1 for children and 8:1 for adults. They found that the precision of
measurements in children was similar to what was found in adults, despite the larger ratio for children. Moreover, Lockner et al. indicate that it might be more difficult to perform the thoracic gas volume measurement procedure in children than in adults, which leads to the use of predicted lung volumes.

The default equations used in BOD POD software are for adults. In a study by Dewit et al., where child-specific equations were used to calculate child-specific thoracic gas volume and BC instead of adult equations, the difference in %BF changed from 0.8% (using the BOD POD software) to −0.9%. This means that the use of adult equations overestimates thoracic gas volume in children. Errors in thoracic gas volume only have a small effect on %BF, as only 40% of thoracic gas volume is involved in the body volume equation. Multi-compartment models were used as the gold standard method against ADP to study its validity in children. While some researchers reported a good degree of accuracy for ADP compared to multi-compartment models, Parker et al. reported that ADP has a large bias compared to the 3-C model in children. Fields and Goran compared the %BF using the BOD POD and other methods against the 4-C model in children. They found that the BOD POD significantly underestimated %BF with a difference of −2.7%, but HD was also found to underestimate %BF with a difference of −3.9% between the two methods. It is valuable to note that in other analyses of the methods mentioned in this study, it was shown that the BOD POD was the only method that showed no trend to underestimate %BF in children with lower fatness and to underestimate %BF in children with higher fatness.

Of note, the PEA POD is used for infants weighing up to 8 kg and to about 6 months of age, while the BOD POD can be used for children who are ages 6 and above. With the TOD POD (a seat designed for toddlers) added to the BOD POD, children between 2 and 6 years can be assessed. However, there is a gap for using the ADP technique in the age group from 6 months to 2 years. There is still no device available for this age group.

2.4.7.1.3 Studies in Infants

Studies on the reliability and validation of the PEA POD have been conducted since 2003. More than 40 articles have been published on using the ADP technique in infants. While a number of these studies were performed on full-term infants, a few were conducted on preterm and sick infants, mainly to determine outcome variables, track growth, or understand the effects
of certain diseases on BC. The first paper was published in 2003 by Urlando et al. In this study, five volume phantoms and three different weights were used to test the ability of the PEA POD© to accurately measure volume and mass. Both the volumes and weights used were representative of infants between birth and 6 months of age. For repeated mass measurements, the largest mean values differed by ≤0.1 g from the actual mass values, indicating high precision and accuracy of the PEA POD© scale. For repeated volume measurements, standard deviation (SD) values ranged between 1.1 and 4.5 mL, and CV values ranged between 0.02 and 0.09%, which indicate a high level of precision.

A validation study that followed used 24 known bovine tissue phantoms ranging in mass (1.3894–9.9516 kg) and %fat (2.08–34.40%) to compare the PEA POD© with chemical analysis (CA) and HD. The study showed mean values of fat content of 18.55% from ADP and 18.59% from CA, and thus no significant difference in %fat between the two methods. In addition, %fat measurements obtained with ADP, CA, and HD were highly correlated ($r > 0.99, P < 0.0001$).

On the heels of this study, Yao et al. published a paper in 2003 presenting a preliminary evaluation of within- and between-day reliability of the ADP system using 17 human infants (ranging from 1 to 22 weeks) tested three times over two days. The study showed that mean differences in %BF of within- (-0.39±0.81) and between-day tests (-0.27±0.97) did not significantly differ from zero, representing the ability of the ADP system to reliably measure %BF in infants.

The largest reliability and validation study to date included 80 infants (ranging from 0.4 to 22 weeks) and was completed between the United States and China. The study was divided into two portions: the reliability study, which included 36 infants, and the validity study, which included 53 infants. %BF was compared using ADP against the deuterium dilution method in the validity portion. The reliability study showed that the mean between- and within-day test-retest SDs of 0.69% and 0.72%BF, respectively, indicated excellent reliability. The mean between-test %BF obtained from ADP also didn’t differ from values of %BF obtained from the reference method in the validity study.

The validity of the PEA POD© was also tested against a 4-C reference model. In 2007, Ellis et al. performed the first study that compared %BF values using the PEA POD© with values from a 4-C model as the reference method. The mean difference was not significant (0.6 %BF), which
shows a good agreement between the two methods. Moreover, the mean difference between repeated tests of the PEA POD© was 0.4 %BF only, which indicates the excellent reliability of the PEA POD© 177.

In a 2012 study by Roggero et al., %fat estimated by the PEA POD© was validated against values estimated by ²H₂O dilution in preterm infants, resulting in high precision and good validity 178.

In the same year, Fields et al. published their data on the first study to compare BC values from DXA and ADP in infancy, since it is less common to use DXA as an assessment tool in children under 2 years. Estimates of %fat from ADP were significantly lower than estimates from DXA. However, this finding is consistent with findings from studies of older children that compare %fat measured by ADP and DXA 179. Further, longitudinal reference BC data (%fat, FM, and FFM) using ADP for exclusively breast-fed infants from 0 to 6 months was published by Fields et al. in 2011 13.

Based on the aforementioned studies performed to test the ADP technique’s reliability and validation in the infant group, it is clear that the technique shows a promising future as a BC assessment tool. Table 2-1 categorizes the relevant literature that the use of ADP to assess BC in infancy by number of subjects studied, age, and method used. The table also highlights the major conclusions drawn by each study.
Table 2-1: Summary of Literature Pertaining to Infant BC Measurement Using the PEA POD©.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects no.</th>
<th>Age</th>
<th>Method Used</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al. (2011) 180</td>
<td>350 (Ethiopian newborns)</td>
<td>Term infants (measurements were taken within 48 h of birth)</td>
<td>ADP¹</td>
<td>Reference data on birth FM² and FFM³ from a low-income setting</td>
</tr>
<tr>
<td>Law et al. (2011) 181</td>
<td>87 mother/infant pairs</td>
<td>3 groups: 1) EFW⁴ less than 10⁰th percentile 2) EFW⁴ greater than the 10⁰th percentile, but AC⁵ less than the 5⁰th percentile 3) EFW⁴ greater than the 10th percentile, &amp; AC⁵ greater than the 5⁰th percentile (normal controls)</td>
<td>Prenatal US⁶ assessment + ADP¹</td>
<td>%BF was lower in group (1) infants compared to group (2) infants. An AC⁵ of less than the 5⁰th percentile on US⁶ doesn’t reflect the same severity of IUGR⁷ as EFW⁴ less than 10⁰th percentile.</td>
</tr>
</tbody>
</table>
| Lingwood et al. (2012) 51  | 77           | Term Infants (measurements done over the first 4 months) | BIA⁸ + ADP¹ + skinfold thickness | • Before 3 months: BIA⁸ didn’t show any improvement over anthropometrics in estimating FFM³ & FM².  
• At 3-4.5 months: BIA⁸ showed improvement in estimating FFM³ with small bias.  
• Skinfold thickness performed poorly.  
• ADP¹ is the ideal way for assessing BC⁹ in infants. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lampl et al. (2012)</td>
<td>220 non-Hispanic Caucasian &amp; 93 non-Hispanic African American Newborns</td>
<td>ADP&lt;sup&gt;1&lt;/sup&gt;</td>
<td>African American neonates had a lower birth weight and lean mass, with a similar FM&lt;sup&gt;2&lt;/sup&gt; compared with Caucasians.</td>
</tr>
<tr>
<td>Andres et al. (2012)</td>
<td>65 (46 lean mothers, 19 overweight mothers) Term infants (measurements done over the first 2 weeks of life)</td>
<td>ADP&lt;sup&gt;1&lt;/sup&gt; + anthropometric measurements</td>
<td>Infants of overweight mothers have more FM&lt;sup&gt;2&lt;/sup&gt; than infants of lean mothers.</td>
</tr>
<tr>
<td>Moyer-Mileur et al. (2009)</td>
<td>47 mother/infant pairs</td>
<td>Fetal biometrics (2-D US&lt;sup&gt;6&lt;/sup&gt;) + anthropometric measurements + ADP&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Biometric data obtained from 2-D US&lt;sup&gt;6&lt;/sup&gt; is not a reliable method in assessing %BF in full-term infants.</td>
</tr>
<tr>
<td>Lee et al. (2009)</td>
<td>324</td>
<td>Anthropometrics measurements + ADP&lt;sup&gt;1&lt;/sup&gt;</td>
<td>FM&lt;sup&gt;2&lt;/sup&gt; and %BF increased with increasing total weight. %BF was greater in females. %BF &amp; FM&lt;sup&gt;2&lt;/sup&gt; were greater in African American neonates than in Caucasians.</td>
</tr>
<tr>
<td>Hawkes et al. (2011)</td>
<td>734</td>
<td>Anthropometric measurements + ADP&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Male infants have higher BW&lt;sup&gt;10&lt;/sup&gt;, but lower %BF than females. Increasing gestation and maternal BMI&lt;sup&gt;11&lt;/sup&gt; lead to increased %BF in infants.</td>
</tr>
<tr>
<td>Deierlein et al. (2012)</td>
<td>128</td>
<td>Anthropometric measurements + ADP&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Male infants have higher BW&lt;sup&gt;10&lt;/sup&gt;, but lower %BF than females. Skinfold thickness doesn’t provide information on visceral fat. Currently, it is limited to estimate FM&lt;sup&gt;2&lt;/sup&gt; in early infancy.</td>
</tr>
<tr>
<td>Andres et al. (2012)</td>
<td>113</td>
<td>ADP&lt;sup&gt;1&lt;/sup&gt; + DXA&lt;sup&gt;12&lt;/sup&gt; + QNMR&lt;sup&gt;13&lt;/sup&gt;</td>
<td>In infants, FM&lt;sup&gt;2&lt;/sup&gt; is overestimated when using QNMR&lt;sup&gt;13&lt;/sup&gt; compared to DXA&lt;sup&gt;12&lt;/sup&gt; or ADP&lt;sup&gt;1&lt;/sup&gt;.</td>
</tr>
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<sup>1</sup>ADP: Air Displacement Plethysmography; <sup>2</sup>FM: Fat Mass; <sup>3</sup>FFM: Fat Free Mass; <sup>4</sup>EFW: Estimated Fetal Weight; <sup>5</sup>AC: Abdominal Circumference; <sup>6</sup>US: Ultrasound; <sup>7</sup>IUGR: Intra Uterine Growth Restriction; <sup>8</sup>BIA: Bioelectrical Impedance Analysis; <sup>9</sup>BC: Body Composition; <sup>10</sup>BW: Body weight; <sup>11</sup>BMI: Body Mass Index <sup>12</sup>DXA: Dual-Energy X-ray Absorptiometry <sup>13</sup>QNMR: Quantitative Nuclear Magnetic Resonance.
2.5 Gastrochisis

Gastrochisis is a congenital abnormality of the abdominal wall through which the abdominal contents of the developing fetus extrude into the amniotic space\textsuperscript{189}. It is usually detected during pregnancy by ultrasound and serum screening of the mother. Gastrochisis is typically an isolated defect which is not associated with other anomalies\textsuperscript{190}. For treatment, infants require either primary surgical closure or serial reductions of herniated viscera followed by surgical or non-surgical closure. However, reported rates of survival are now more than 90\% for infants with this condition\textsuperscript{191}.

The incidence of gastrochisis has been increasing worldwide, including Canada. According to the Canadian Congenital Anomalies Surveillance System (CCASS), the rate of gastrochisis in Canada has increased by a percentage of 43.8 from 2002 to 2009\textsuperscript{192}.

The cause of gastrochisis is still unknown. However, it has been associated with several maternal risk factors, including age, undernutrition, Caucasian ethnicity, smokers, alcohol abuse, and illicit drug use\textsuperscript{192}.

Despite the high survival rate in gastrochisis infants, being diagnosed with this anomaly will increase the risk of stillbirth, premature birth, intrauterine growth restriction (IUGR), low birth weight, fetal distress, and prolonged hospitalization\textsuperscript{193,194}. Moreover, oral feeding is delayed for a variable period due to associated intestinal dysmotility. The decision regarding their readiness for enteral nutrition initiation is based on the infant’s clinical status (abdominal distension and gastrointestinal function). However, Sharp et al. has suggested that early enteral feeds might be beneficial for these infants\textsuperscript{195}. Due to the aforementioned factors, infants with gastrochisis rely on parenteral nutrition (PN) for long periods.

Thus, a combination of physiological factors, in addition to the surgical intervention affect nutritional requirements and managements in those infants.
Chapter 3
Rationale, Objectives, and Hypothesis

3.1 Rationale

The optimal growth of a preterm baby is not known. The currently accepted approach is that a baby should achieve growth at a rate and BC that is similar to a normal fetus of the same gestational or postmenstrual age.\(^5,196\)

Due to the numerous issues associated with the average preterm infant, the reality is that very few, if any, neonatal intensive care units (NICU) can boast of achieving this target set over 20 years ago. A recent systematic review and meta-analysis showed that most preterm infants still have a lower proportion of lean mass—and thus a higher proportion of fat—than their term counterparts. They are generally lighter, shorter, and have smaller head circumferences.\(^5\)

This may be due to preterms being given more energy than needed, with a resulting high body fat content. In addition, if insufficient amino acids are supplemented, the lean body mass—muscle and bone—would be underdeveloped.\(^197\)

Gastroschisis is a congenital anomaly that affects the anterior abdominal wall, causing evisceration of the intra-peritoneal contents.\(^189\) The incidence of gastroschisis has been increasing worldwide, including in Canada. However, the reason behind this increase is unclear.\(^192\)

This physiological defect affects infants’ nutritional requirements and growth. Infants with gastroschisis are born late preterm with low birth weights. Their enteral nutrition is delayed because of associated GI symptoms. They rely on PN for long periods. Therefore, it is valuable to measure the BC in this group of infants to investigate the reason behind their low weights and to evaluate and reassess their current nutritional requirements.

The ADP technique is a relatively new BC technique for use in infants. Available studies were performed mainly on healthy term infants, with very few performed on preterm infants. There are almost no studies on sick infants using this technique. It is novel for us to be able to use this technique and measure BC in this high-risk group of infants. To our knowledge, this is the first
study that measures BC in gastroschisis infants. Using the PEA POD\textsuperscript{©} in our study further adds to its novelty.

3.2 Objectives

The objectives of this study were twofold: (1) to evaluate the feasibility and acceptability of the ADP technique using the PEA POD\textsuperscript{©} in a high-risk group of patients with the comparison to healthy reference infants, and (2) to evaluate the BC of our surgical infants with gastroschisis post-operatively using ADP.

3.3 Hypothesis

We hypothesize an altered BC in gastroschisis infants compared to healthy reference infants.
Chapter 4
Methodology

4.1 Subjects
All infants greater than or equal to 33 weeks’ gestational age (GA) diagnosed with gastroschisis and admitted to the NICU at the Hospital for Sick Children were screened for eligibility. Parents of eligible infants were approached; the study was explained to them by me with an information sheet provided. The sample size in this study was determined depending on the number of gastroschisis cases admitted to the NICU of the Hospital for Sick Children.

4.1.1 Study Inclusion Criteria
The inclusion criteria for this study involved all infants ≥ 33 weeks GA at birth with a confirmed diagnosis of gastroschisis. An informed consent was also obtained from all parents.

4.1.2 Study Exclusion Criteria
When parents were unable to obtain informed consent or when the patient was too unwell, i.e., needing supplemental oxygen or unable to be transported, they were excluded from this study.

4.2 Study Design
This was a prospective-observational (cohort) study over a one-year period in the NICU at the Hospital for Sick Children. Data collected from this study were compared to reference data available from the literature\(^1\). The participant infants received standard care for management of gastroschisis as directed by the responsible neonatologist, surgeon, and dietitian. Generally, infants were transferred on day 1 of life to The Hospital for Sick Children, an outborn unit, and medically treated with either primary closure or serial reduction with silo over a period of days, depending on the size of the abdominal defect. They were started on PN as soon as they were admitted to the hospital with the hold of enteral feeds until intestinal motility and health was regained after abdominal closure.

4.2.1 Body Composition Measurement
BC measurements using the PEA POD\(^\circ\) device took place at the clinical research center (CRC), known previously as the physiological research unit (PRU), at the Hospital for Sick Children.
The PEA POD© is the tradename of the device that uses the ADP technique for infants. This device is approved by Health Canada to measure BC in infants between 1 and 8 kg. More details about the PEA POD© will be discussed in the following subsections.

4.2.1.1 PEA POD© - System Description

PEA POD© components are contained in a movable cart that is supported with locking casters that makes the device mobile and easy to be placed in different locations. The reference chamber, calibration volume, air circulation and heating system, electronic components, printer, central processing unit (CPU), and calibration volume phantom are all housed in the movable cart. The test chamber, scale tray, and monitor/computer are outfitted on the top surface of the cart. The two chambers (test and reference) are connected with an oscillating diaphragm and a calibration valve. The calibration valve allows the testing chamber to be connected to the known reference calibration volume. Pressure transducers are connected to the two chambers. In addition, the device is supported with air circulation and temperature systems that keep the air circulating continuously from the outside environment to the test chamber at a temperature of 31°C. The test chamber contains a sliding plastic tray where the subject is placed and covered with a plastic shield. It is designed to protect the subject from falling out of the tray. An electromagnet system is used to keep the test chamber’s door closed during the test. It is also supported with a cancel test button and an emergency stop knob to stop the test and remove the subject at any time during the test. Figure 4-1, Figure 4-2, and Figure 4-3 below show the PEA POD© device from different views.
Figure 4-1: An Angular-Zoomed-out View of the PEA POD® Device
Figure 4-2: A Zoomed-in Front View of the PEA POD® Device
Figure 4-3: A Picture Showing the Sliding Chamber where the infants are placed
4.2.1.2 PEA POD© - Operating Principles

The PEA POD© device uses the principle of whole body densitometry. Densitometry is based on using Db to derive BC by measuring body mass and body volume. In the PEA POD© device, body mass is measured using an electronic scale, and body volume is measured in the test chamber by applying Boyle’s and Poisson’s laws relating pressure changes to volume of air in the chamber. After the subject’s mass and volume are measured, Db can be calculated easily. From Db, %fat is calculated, assuming a constant density of fat. On the other hand, because FFM changes constantly, the PEA POD© uses age- and gender-specific densities of FFM obtained from studies available in the literature 1,2. Finally, %fat, %FFM, FM, and FFM values are displayed on the PEA POD© computer screen.

4.2.1.3 PEA POD© - Personnel Training

All staff and nurses in the CRC who dealt with or used the PEA POD©—plus the research team, myself included—received training and consultation sessions by a COSMED, USA representative. Around 60 PEA POD© tests are performed per year at the Hospital for Sick Children, mainly for research purposes. The manufacturer representative visits the CRC annually and spends around 2.5 hours checking the PEA POD© device in terms of calibration, software upgrade, air filters changing, and overall device checkup. The visit also includes a troubleshooting session to discuss problems or difficulties facing the staff who use the PEA POD© device.

Further practice was performed by the staff and the research team on the PEA POD© using phantoms to gain more familiarity and expertise using this new device before it was used with human subjects.

4.2.1.4 PEA POD© Calibration

The PEA POD© needed to be turned on at least two hours prior to testing to warm up and to allow the test chamber to reach 31°C. Daily quality control tests were performed, including scale and test chamber calibrations. The scale was calibrated as instructed by the PEA POD© computer using the 2kg weight provided with the device. Volume calibration in the test chamber was performed using the volume phantom provided. Once quality control was complete, infant information was entered to the computer, including the name, GA, date of birth, gender, and
length. Infants cannot be attached to any external monitors or intravenous pumps such as PN during the test. The infant was checked for any medical equipment that couldn’t be removed for the test and that would alter the infant’s weight/volume including an intravenous line (IV), nasogastric tube (NGT), gastrostomy tube (GT), peripherally inserted central catheter (PICC) line, or wound dressing. An equivalent for the item was used to calibrate the PEA POD® in order that the volume and weight of the equipment was accounted for.

4.2.1.5 Subject Preparation and ADP Measurement

BC measurement took place in the CRC. Gastroschisis infants were transported to the unit in their cribs by a transport clerk, the bedside registered nurse, and me. The bedside registered nurse prepared the infant for the test by undressing him/her, including diaper removal, flattening the hair using a damp cloth for infants with little hair or baby oil for those with large amounts of hair, and heparin-locking any IV lines. Sucrose drops were used to calm the infants immediately before the test. Test step instructions were displayed on the PEA POD® computer and were followed by me with the support of staff in the CRC. First, the infant was placed on the PEA POD® scale for mass measurement. Then, he/she was placed inside the warm test chamber for approximately 2 minutes for body volume measurement. The infant was visible continuously, and the level of CO₂ was monitored automatically during the test to ensure there was no re-breathing during the test. After the test was completed, the test chamber’s door opened automatically and the infant was removed and returned to his/her crib. Finally, the scale and the test chamber’s tray were cleaned and allowed to air dry after each use. The whole test starting from placing the infant on the measuring scale took from 5 to 7 minutes.

4.2.2 Data Collection and Study Timeline

Data were collected from infants’ medical records (charts or the software system at the hospital known as Kidcare) by maternal interviews, either in person or by phone, and by talking personally to the medical caregivers who were in charge of the infants if more details were needed. Variables including GA at birth, date of birth, birth weight, birth length, birth head circumference, gender, diagnosis, illness severity, date and type of gastroschisis abdominal closure, nutritional information, and laboratory results were collected from infants’ medical records. However, since mid-upper-arm circumference (MUAC) is not one of the routine anthropometric measurements taken at birth, it was not included within the birth measurements
for this study. When more information or clarification was needed about the case, either medically or nutritionally, the nurse or the dietitian in charge was contacted. Maternal information including age, weight, height, illnesses, medications, marital status, and the infant’s order in the family was recorded by maternal interviews or from medical records.

Data were collected to assess the subjects’ eligibility, to compare subjects’ status/outcomes with available literature on the same group studied here and with reference data, and to compare findings on different outcomes throughout the study.

All infants had their gastroschisis closure within the first week after birth, except for one infant who had his on day 8 of life. The decision about the time for the first PEA POD® was all dependent on the medical stability of the infant. The aim for performing the second PEA POD® was planned to be one month after the first.

Before each PEA POD® test, crown-heel length, head circumference (HC), and MUAC on the left arm were measured using a plastic measuring tape and were recorded by the researcher in centimeters to the nearest ± 0.1 cm.

Two BC measurements were taken using the PEA POD® for this study. The first was taken when the infants were extubated post-operatively and medically stable for the procedure, i.e., not having spells, hemodynamically stable, off supplemental oxygen, and not on continuous infusions such as inotropes. However, for infants who were still on PN, it was stopped for the duration of the test. A total of 12 infants completed the first PEA POD® successfully while they were hospitalized at the Hospital for Sick Children. Seven were able to follow up with the second PEA POD® measurement (4 were already discharged from the hospital and came back for the test, and 3 were still hospitalized). The other 5 didn’t perform the second PEA POD® measurement, either because they live far away from Toronto or because they simply did not respond to reminder calls about the second PEA POD®.

BC data in this study was compared to reference data from available literature. A longitudinal BC study that was done on 160 exclusively breast-fed healthy infants from birth to 6 months of age using the ADP technique was chosen as reference data for this study. BC data for this study involved values of %FM, FM, and FFM. Z-scores were used in the comparison between BC parameters to normalize for GA, and a Z-score calculator was used for this calculation.
Moreover, MUAC data was compared to normative data from a study that was done on 81 healthy-term infants and was chosen as a reference.\textsuperscript{198}

### 4.2.2.1 Nutritional Information

All infants were fed enterally and parenterally according to the standard unit protocol. Preterm infants were started on an initial PN dose of 1.5–2.5 g/kg/d amino acids, 0.5–1 g/kg/d lipids, and 5–8 mg/kg/min dextrose with a goal of 3.5–4 g/kg/d amino acids, 3 g/kg/d lipids, and 10–16 mg/kg/min dextrose. Term infants were started on 1.5–2 g/kg/d amino acids with the same lipids and dextrose doses as for preterm infants, with a goal of 2.5–3.5 g/kg/d amino acids, 11–12 mg/kg/min dextrose, and the same lipids goal as for preterm infants. Trials of enteral feeds were started depending on the infant’s health, intestinal motility, and tolerance. The feeding options included mother’s own milk, donor expressed breast milk for eligible infants, Enfamil premature A+ formula with iron for infants < 2 kg, and Enfamil A+ formula with iron for infants > 2 kg.

Enteral and parenteral nutritional information were recorded for all infants at first and second PEA POD\textsuperscript{©} measurements. For enteral feedings, this included the route of feeding (oral, NGT, or GT), the type of feeding (breast milk, formula, or both), the total daily volume (TDV) from enteral feeds in milliliters per day (ml/d), the calories from enteral feeds in kilocalories per kilograms per day (kcal/kg/d), and the fortification concentration if added to the original feeds. For PN, that included the TDV from PN in ml/d, the energy intake in kcal/kg/d, the protein intake in grams per kilograms per day (g/kg/d), the fat intake in g/kg/d, the TDV from SMOF lipids in ml/d, the calories from SMOF lipids in kcal/kg/d, and the total fluid intake (TFI) from PN and SMOF lipids in ml/d.

Further, laboratory values were recorded at the time of each PEA POD\textsuperscript{©} measurement from PN biweekly blood test results. These included calcium, phosphorus, alkaline phosphatase, creatinine, urea, albumin, red blood cells, and hemoglobin levels.

### 4.3 Data Analysis

BC data were compared to normative data from the available literature.\textsuperscript{13} Anthropometric data were compared to Fenton’s growth charts, using a Z-score calculator.
Means and standard deviations were first calculated using Microsoft Excel (2011). Afterwards, a paired $t$-test was used to compare our values on anthropometrics and BC with reference values and test the significance between the two groups. $T$-test was used to assess $Z$-scores and test the significance. $P \leq 0.05$ was deemed statistically significant.
Chapter 5
Results

5.1 Subjects’ Recruitment

Thirty-one infants were admitted to the hospital during the period between May 2015 and May 2016 with a diagnosis of gastroschisis. Five were excluded because they were on supplemental oxygen and/or continuous infusions. Thereafter, 26 infants were approached during this period. Written consents were obtained from the parents of 12 infants. Parents of 14 infants declined to participate. The decline was due to a lack of interest in research. Moreover, some infants were already participating in other studies. Only 7 infants of the 12-participating followed up with the second PEA POD®. That was due to the long distance from where they live to the hospital for 3 infants, and the failure to get any response from the other 2. Figure 5-1 illustrates the recruitment process.
Figure 5-1: Subjects’ Recruitment Flowchart
5.2 Patient Characteristics

A total of 12 infants (boys =7), ≥33 weeks GA at birth who were diagnosed with gastroschisis were enrolled in this study. The mean GA at birth was 36.2±1.3 weeks, mean birth weight was 2.4±0.5 kg, mean birth length was 45.2±3.1 cm, and the mean birth HC was 32.3±1.7 cm. Information on subject characteristics at birth is summarized in Table 5-1.

<table>
<thead>
<tr>
<th>GA (weeks)</th>
<th>BW (kg)</th>
<th>Length (cm)</th>
<th>HC (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>36.2</td>
<td>2.41</td>
<td>45.2</td>
</tr>
<tr>
<td>SD</td>
<td>1.31</td>
<td>0.55</td>
<td>3.14</td>
</tr>
<tr>
<td>Median</td>
<td>36.45</td>
<td>2.28</td>
<td>45</td>
</tr>
<tr>
<td>IQR</td>
<td>2.07</td>
<td>0.96</td>
<td>5.5</td>
</tr>
</tbody>
</table>

1GA: gestational age; 2BW: body weight; 3HC: head circumference; 4SD: standard deviation; 5IQR: interquartile range.

5.3 Clinical Data

All infants underwent a gastroschisis repair with either primary closure or serial reduction with silo. 2/12 infants performed primary closure of the gastroschisis defect on day 1 of life. The other 10/12 had serial reductions followed by a closure within the first 8 days of life. The mean gastroschisis defect size was 2 cm. The mean age for the final gastroschisis repair was 3.8±2.6 days.

All infants were on PN as soon as they were admitted to the hospital (within the first 3 days of life). The mean for PN duration was 47 days, ranging from 9 to 195 days. As mentioned above, enteral nutrition is delayed in those infants, and enteral intake attempts are started according to the infants’ gastrointestinal health. The mean nothing per oral (NPO) duration was 17 days, ranging from 4 to 55 days.

As described, two BC measurements were performed using the PEA POD© for this study. The age at first PEA POD© assessment was 25.5±8.4 days and 22±6.2 days after the gastroschisis repair. There was considerable range in age due to the infants’ medical stability and the availability of the device.
The mean time between the 2 PEA POD© assessments was 50±45 days. Several external factors affected this timing, including the medical status of the infant, the presence of other medical procedures that delayed the PEA POD© measurement, and the arrangement for the PEA POD© to be used on the same day of other doctors’ appointments for discharged infants for parents’ convenience. For all infants who were followed up, the duration between the two PEA POD© measurements ranged from 12 to 148 days. BC data for gastroschisis infants from this study was compared to BC data of a group of exclusively breast-fed healthy infants from the literature13.

5.4 Maternal Characteristics

All mothers’ demographic data were collected through maternal interviews or from medical records. Mothers’ mean age was 25.5±5.3 years (83% of the mothers were ≥20 years of age), mean weight at first prenatal visit was 73.05±19.9 kg, mean height at first prenatal visit was 166.5±9.5 cm, and mean BMI at first prenatal visit was 26.35±6.4 kg/m². Of the 12 mothers, 3 were married, 3 were single, and 4 were in a relationship. The marital status plus the weight, height, and BMI were not recorded for 2 mothers. Of the 10 mothers for whom we have BMI measurements, 6 were overweight, 2 were normal, 1 was underweight, and 1 was obese. Fifty percent of the mothers were first-time mothers.

All mothers were on prenatal vitamins, and none had diabetes mellitus. However, 3 mothers of the 12 had coexisting health issues including hypothyroidism, polycystic ovary syndrome, depression, anxiety, anemia, and renal stones. Medications taken included synthroid, thyroxine, prednisone, iron supplements, and antibiotics. Further information of maternal characteristics is summarized in Table 5-2.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>BW¹ (kg)</th>
<th>Height (cm)</th>
<th>BMI² (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>25.5</td>
<td>73.05</td>
<td>166.5</td>
<td>26.35</td>
</tr>
<tr>
<td>SD³</td>
<td>5.36</td>
<td>19.97</td>
<td>9.54</td>
<td>6.49</td>
</tr>
<tr>
<td>Median</td>
<td>25.5</td>
<td>68.5</td>
<td>166</td>
<td>25.5</td>
</tr>
<tr>
<td>IQR⁴</td>
<td>10.25</td>
<td>15</td>
<td>17.5</td>
<td>4.37</td>
</tr>
</tbody>
</table>

¹BW: body weight; ²BMI: body mass index; ³SD: standard deviation; ⁴IQR: interquartile range.
5.5 Growth Parameters at Birth

Birth growth parameters including weight, length, and HC were recorded from infants’ medical records and then compared to Fenton’s preterm growth charts according to sex and age.

The average wt. Z-score at birth was -0.81, ranging from -3.12 to 0.90, with 10 negative values out of the 12. This indicates significantly lower birth weights for gastroschisis infants in this study compared to reference preterm infants for the same age and sex (p=0.01). For the length, the average Z-score at birth was -0.84, ranging from -2.61 to 0.90, with 9 negative values out of the 12. This also indicates significant low birth lengths for infants in this study compared to reference infants (p=0.01).

However, there was no significant HC difference between infants in this study and reference infants (p=0.18). The average HC Z-score was -0.27, ranging from -1.89 to 1.41, with 8 negative values out of the 12.

This indicates that the infants included in the study had asymmetric intrauterine growth restriction (IUGR).

5.6 Body Composition and Anthropometry at First PEA POD©

5.6.1 Anthropometry at first PEA POD©

The first PEA POD© assessment could not be performed until the infant was medically stable and off any continuous infusions, including oxygen therapy.

At the first PEA POD©, average wt. Z-score was -1.23±1.2, ranging from -3.55 to 0.14, and average length Z-score was -1.7±1.5, ranging from -4.53 to 0.29, still significantly lower compared to reference infants (p=0.002) for weight and (p=0.001) for length. Moreover, when compared to Z-scores at birth, infants’ weight and length Z-scores decreased significantly from birth to first PEA POD© with (p=0.003) and (p=0.006) respectively. This means that the weight and length had not increased at an appropriate rate for these infants during this time range.

However, the average HC Z-score at the first PEA POD© was -0.32±1.1, ranging from -2.33 to 1.91, which shows no significant difference when compared to reference infants (p=0.1). Also, when compared to HC Z-scores at birth, Infant HC appeared to be maintained (p=0.7).
Table 5-3 shows the Z-score values for wt., length, and HC at birth and at first PEA POD© measurement for all subjects in this study.
Table 5-3: Z-scores for Wt\(^1\), Length, and HC\(^2\) at Birth and 1st PEA POD\(^©\) Measurements

<table>
<thead>
<tr>
<th>Subject</th>
<th>wt. Z-scores</th>
<th>Length Z-scores</th>
<th>HC Z-scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Birth</td>
<td>1(^{st}) PEA POD(^©)</td>
<td>Δ</td>
</tr>
<tr>
<td>1</td>
<td>0.90</td>
<td>-0.00</td>
<td>-0.91</td>
</tr>
<tr>
<td>2</td>
<td>-1.59</td>
<td>-1.79</td>
<td>-0.20</td>
</tr>
<tr>
<td>3</td>
<td>-0.11</td>
<td>-0.38</td>
<td>-0.27</td>
</tr>
<tr>
<td>4</td>
<td>-0.08</td>
<td>-0.12</td>
<td>-0.03</td>
</tr>
<tr>
<td>5</td>
<td>-1.31</td>
<td>-1.91</td>
<td>-0.60</td>
</tr>
<tr>
<td>6</td>
<td>-0.81</td>
<td>-1.06</td>
<td>-0.25</td>
</tr>
<tr>
<td>7</td>
<td>0.55</td>
<td>0.14</td>
<td>-0.41</td>
</tr>
<tr>
<td>8</td>
<td>-3.12</td>
<td>-3.55</td>
<td>-0.43</td>
</tr>
<tr>
<td>9</td>
<td>-1.39</td>
<td>-1.77</td>
<td>-0.38</td>
</tr>
<tr>
<td>10</td>
<td>-0.62</td>
<td>-0.88</td>
<td>-0.25</td>
</tr>
<tr>
<td>11</td>
<td>-1.71</td>
<td>-3.10</td>
<td>-1.38</td>
</tr>
<tr>
<td>12</td>
<td>-0.42</td>
<td>-0.39</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.81</td>
<td>-1.23</td>
<td>-0.42</td>
</tr>
<tr>
<td>SD(^3)</td>
<td>1.10</td>
<td>1.21</td>
<td>0.39</td>
</tr>
</tbody>
</table>
¹Wt: weight; ²HC: head circumference; ³SD: standard deviation.
5.6.2 Body Composition at First PEA POD®

5.6.2.1 Nutritional Data

At the time of the first PEA POD®, 9 of the 12 infants were on NGT feeding, 2 of 12 were on oral feeds, and 1 of 12 was NPO. All of the infants except the one who was NPO were taking expressed breast milk (EBM), either from the mother’s own milk or from donor milk. Formula was given only on occasions when EBM was insufficient. Only one infant had fortified feeds. Nine of the 12 infants (not necessarily the same 9 that were on NGT) were on PN, while the other 3 were already weaned from PN. The nutritional information from PN in averages was as follows: energy: 58 kcal/kg/d, protein: 3 g/kg/d, fat: 2.8 g/kg/d, TDV: 315.4 ml/d, and 28.59 kcal/kg/d from SMOF lipids.

5.6.2.2 Body Composition Data

5.6.2.2.1 %Fat Mass

At the first PEA POD®, the average %FM Z-score was 0.93±1.7, ranging from -1.99 to 3.88, which indicated a significantly higher %FM for infants in this study compared to reference infants (p=0.04).

5.6.2.2.2 Fat Mass

Absolute FM Z-score was 0.41±1.7, ranging from -2.08 to 3, which did not show a significant increase in FM compared to reference infants; it was comparable (p=0.2).

5.6.2.2.3 Fat Free Mass

For FFM, average Z-score was -1.42±1.2, ranging from -3.68 to 0.26. This showed that FFM was significantly lower in infants in this study than in reference infants (p=0.0009).

Figure 5-2 shows the FM and FFM Z-scores for all 12 infants in this study at the first PEA POD®.
Figure 5-2: Bar Chart represents BC parameters for all infants participating in the first PEA POD© study.

The figure above shows that all infants had FFM Z-scores lower than the mean reference value, except for one infant (subject 7) with a Z-score of 0.26. This infant was NPO for 9 days since birth, then transferred to NGT feeding at a rate of 22ml every 3 hours of EBM. He was slowly progressing in reaching his goal feeds (80ml every 3 hours). He was depending mainly on PN for nutrition, with the highest TDV of 518.4 ml/d among all other infants. He was on 64 kcal/kg/d energy, 3.6 g/kg/d protein, and 3 g/kg/d fat.

5.7 Body Composition and Anthropometry at Second PEA POD©

5.7.1 Anthropometry at Second PEA POD©

The second PEA POD© assessment was performed an average of 50±45 days after the first. At the second PEA POD©, average wt. Z-score was -1.48±1.3, ranging from -3.51 to 1.12, and average length Z-score was -1.58±1.5, ranging from -4.52 to 0.04. This shows that infants in this study are still significantly lower for both weight and length Z-scores compared to reference infants (p=0.01). However, the average HC Z-score was -0.20±1.3, ranging from -2.5 to 1.44, which shows no significant difference when compared to reference infants (p=0.3). Table 5-4
shows all Z-score values for wt., length, and HC at the first and second PEA POD© measurements for all subjects in this study.
Table 5-4: Z-scores for Wt\(^1\), Length, and HC\(^2\) at 1st & 2nd PEA POD\(^\circ\) Measurements

<table>
<thead>
<tr>
<th>Subject</th>
<th>1(^{st}) PEA POD(^\circ)</th>
<th>2(^{nd}) PEA POD(^\circ)</th>
<th>Δ</th>
<th>1(^{st}) PEA POD(^\circ)</th>
<th>2(^{nd}) PEA POD(^\circ)</th>
<th>Δ</th>
<th>1(^{st}) PEA POD(^\circ)</th>
<th>2(^{nd}) PEA POD(^\circ)</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.00</td>
<td>1.12</td>
<td>1.12</td>
<td>-0.2</td>
<td>0.04</td>
<td>0.24</td>
<td>0.07</td>
<td>1.44</td>
<td>1.37</td>
</tr>
<tr>
<td>2</td>
<td>-1.79</td>
<td>-1.68</td>
<td>0.11</td>
<td>-1.52</td>
<td>-1.51</td>
<td>0.00</td>
<td>-0.51</td>
<td>0.88</td>
<td>1.39</td>
</tr>
<tr>
<td>5</td>
<td>-1.91</td>
<td>-1.95</td>
<td>-0.03</td>
<td>-2.40</td>
<td>-2.19</td>
<td>0.21</td>
<td>-1.40</td>
<td>-0.62</td>
<td>0.78</td>
</tr>
<tr>
<td>6</td>
<td>-1.06</td>
<td>-1.03</td>
<td>0.02</td>
<td>0.29</td>
<td>-0.13</td>
<td>-0.43</td>
<td>0</td>
<td>-0.09</td>
<td>-0.09</td>
</tr>
<tr>
<td>8</td>
<td>-3.55</td>
<td>-3.51</td>
<td>0.04</td>
<td>-4.16</td>
<td>-4.52</td>
<td>-0.35</td>
<td>-2.33</td>
<td>-2.5</td>
<td>-0.16</td>
</tr>
<tr>
<td>9</td>
<td>-1.77</td>
<td>-2.05</td>
<td>-0.28</td>
<td>-2.38</td>
<td>-2.07</td>
<td>0.30</td>
<td>-0.55</td>
<td>-0.96</td>
<td>-0.40</td>
</tr>
<tr>
<td>12</td>
<td>-0.39</td>
<td>-1.29</td>
<td>-0.90</td>
<td>-2.03</td>
<td>-0.69</td>
<td>1.33</td>
<td>1.14</td>
<td>0.43</td>
<td>-0.70</td>
</tr>
<tr>
<td>Mean</td>
<td>-1.50</td>
<td>-1.48</td>
<td>0.01</td>
<td>-1.77</td>
<td>-1.58</td>
<td>0.18</td>
<td>-0.51</td>
<td>-0.20</td>
<td>0.31</td>
</tr>
<tr>
<td>SD(^3)</td>
<td>1.17</td>
<td>1.39</td>
<td>0.60</td>
<td>1.49</td>
<td>1.57</td>
<td>0.58</td>
<td>1.11</td>
<td>1.31</td>
<td>0.86</td>
</tr>
</tbody>
</table>

\(^1\)Wt: weight; \(^2\)HC: head circumference; \(^3\)SD: standard deviation.
From the Z-score values in Table 5-4, anthropometrics was compared between the first and second PEA POD© assessments. It showed no significant difference in wt., length, and HC Z-scores between the first and second PEA POD© measurements, with (p= 0.9, 0.4, and 0.3) respectively.

5.7.2 Body Composition at Second PEA POD©

5.7.2.1 Nutritional Data

At the time of the second PEA POD©, 4 of the 7 infants were on oral feeds, 1 of 7 was on NGT feeding, and 2 of 7 were on GT feeding; 5 of 7 were exclusively breast fed, 1 of 7 was on formula, and 1 of 7 was on mixed feeds (formula + breast milk). One of the breast-fed infants and the one who was on formula were on fortified feeds. At this point, all infants were weaned from PN except for the two who were on GT feeding. The nutritional information from PN in averages was as follows: energy: 35.5 kcal/kg/d, protein: 1.65 g/kg/d, fat: 1.15 g/kg/d, TDV: 162.6 ml/d, and 11.35 kcal/kg/d from SMOF lipids.

5.7.2.2 Body Composition Data

5.7.2.2.1 %Fat Mass

At the second PEA POD©, average %FM Z-score was -0.73±2.0, ranging from -3.93 to 2.63. This indicated a non-significant difference when compared to reference infants (p=0.1).

5.7.2.2.2 Fat Mass

Average absolute FM Z-score was -0.90±2.1, ranging from -3.56 to 3.21. This indicated a non-significant difference when compared to reference infants (p=0.1).

5.7.2.2.3 Fat Free Mass

FFM average Z-score was -1.39±1.3, ranging from -2.76 to 1.44. This showed that FFM was significantly lower in infants in this study than in reference infants (p=0.01).

Figure 5-3 shows the FM and FFM Z-scores for all the 7 infants in this study at the second PEA POD©.
Figure 5-3: Bar Chart represents BC parameters for all infants participating in the second PEA POD© study.

Comparison of BC Z-scores between the first and second PEA POD© measurements for infants who followed up showed that %FM and FM had decreased significantly from the first PEA POD© to the second (p=0.02 and 0.03), respectively. On the other hand, the FFM was maintained (p=0.6), as shown in Figure 5-4 and Figure 5-5.
Figure 5-4: Chart represents FM Z-scores for all subjects who followed-up between the two PEA POD® studies.
Figure 5-5: Chart represents FFM Z-scores for all subjects who followed-up between the two PEA POD© studies.

5.8 Mid Upper Arm Circumference at First and Second PEA POD©

MUAC was first recorded for all subjects at the time of the first PEA POD©, except for one infant due to a technical discrepancy. Average MUAC Z-score for infants in this study was 0.57±2.29, ranging from -4.85 to 3, which shows no significant difference compared to reference infants (p=0.2). Moreover, average MUAC Z-score at the point of the second PEA POD© was 0.47±2.34, ranging from -3.1 to 3.5, which shows no significant difference compared to reference infants (p=0.3). However, when compared to values from the first PEA POD©, it showed that infants had a significant increase in their MUAC Z-scores (p=0.05).
Chapter 6
Discussion

In this chapter, I will discuss the use of the PEA POD© and its utility in such a high-risk group of infants. Then, I will compare our findings on BC with previous studies. Finally, I will present the limitations, strengths, and implications of this study and suggest future research that might add to this field.

6.1 Utility of the PEA POD©

The PEA POD© device at the Hospital for Sick Children in Toronto is one of only three PEA POD© devices in Canada. The others are in Hamilton and Edmonton, Canada. This device is considered a new tool to measure BC, as it is still not used clinically. However, it has been majorly used in research. Since 2011, approximately 60 tests have been performed annually using the PEA POD© at the Hospital for Sick Children, mainly for research purposes.

Although the PEA POD© has been commercially available for several years, published studies on the device and its feasibility are limited. However, in this study we have demonstrated that the use of the PEA POD© is feasible in gastroschisis infants who have had surgery and who are on prolonged PN.

Approximately half of the parents approached refused to participate, this was due to a general reluctance to participate in research. No parent refused the study solely based on the PEA POD© itself. Moreover, some of the infants were already participating in other competing studies, so parents refused to participate based on that. However, the parents were encouraged to view the test, and all found it a positive experience.

For parents who participated it was an enjoyable experience, especially considering that most of them took photos of their infants inside the PEA POD© chamber, and based on their impression after the test was done. In my opinion, the facts that the infant is visible in the chamber and that parents can see their infant during the entire process, in addition to the minimal time inside the chamber (2 minutes), helped in reassuring the parents. Moreover, most infants were calm and happy during the test, except for 2 infants who were crying slightly, but no test needed to be repeated in this study for any reason.
Previous studies using the PEA POD© device on preterm infants have revealed the same findings that we have shown in this study: this technique is safe, practical, and feasible in this group of infants.\textsuperscript{178,199–201} Studies by Roggero et al.\textsuperscript{178} and Brennan et al.\textsuperscript{201} on using the ADP technique on preterm infants stated that they had not interrupted any BC measurement during their studies because of the safety of the infants or their clinical status and that the measurements were well tolerated by all subjects. Moreover, it has been also shown that ADP is feasible in small for gestational age (SGA) preterm infants, and in those as young as 30 weeks’ gestation, by McLeod et al.\textsuperscript{199} and Ramel et al.\textsuperscript{200}. The study by McLeod et al. emphasized that the temperature of the circulating air in the PEA POD© test chamber kept their small preterm infants warm after they were at risk of becoming cold during the weight and length measurements\textsuperscript{199}. However, to our knowledge, there were no studies discussing parental or medical team experience with the PEA POD©.

All research team members received training on how to use the PEA POD©. Step-by-step instructions for performing the test appear on the computer screen. After using the PEA POD© in our study, we found that the instructions were straightforward and easy to follow.

An additional mass and volume calibration step was needed for all infants because of the lines, IVs, and wound dressing attached that could not be removed. An exact equivalent item was used for calibration. Despite these efforts, it is unclear if this adversely affects the measurement and whether it changes body volume. Further study is needed. An anticipated error could be an underestimation of the body volume in those infants due to the higher isothermal effect of air from the gauze attached to their bodies.

In our study, infants were transferred in their mobile cribs from the NICU located on the third floor to the CRC on the fifth floor where the PEA POD© tests took place. At least two persons were needed to move the crib to the CRC. Based on my experience, it may be beneficial to have the PEA POD© device moved to a designated area or room in the NICU. Since the subjects using the PEA POD© are infants up to 8 kg, they will mostly be infants from the NICU. If they were from other wards or departments in the hospital, perhaps they would be more stable to be moved than NICU infants.

The factors mentioned above—including the study acceptance from the parents, the absence of complications during the study, and the medical stability of the infants during the test—show that
the PEA POD© is safe for use in this population. In addition, the limited time of the test, the noninvasive nature of the test, and the ease of using the PEA POD© device by the research team make the PEA POD© device feasible, easy, and practical to use in high-risk infants. This shows that this technique could be introduced and used in clinical settings in different groups of infants.

6.2 Growth Findings

Gastroschisis infants are mostly born late preterm with an increased risk of being small for gestational age (SGA), with birth weight of < 10th percentile 202. They are born with either simple or complex gastroschisis 203. However, 11 of 12 infants in this study were born with healthy-intact bowels (simple gastroschisis), with one infant needing a subtotal colectomy (complex gastroschisis).

In this study, we have shown that gastroschisis infants have lower birth weight and length than healthy preterm infants; 41.6% of our infants have birth weight < 10th percentile, which agrees with previous studies 204–207. In addition, the mean birth weight in infants in this study was 2.4kg, which approximately matches the mean presented in previous literature for gastroschisis infants 202,208,209.

It has been documented that almost all gastroschisis infants are born with a degree of IUGR, even when the birth weight is > 10th percentile 202,208. IUGR is divided into two categories: asymmetric IUGR—defined as a smaller abdominal size compared to head size—and symmetric IUGR, characterized by a decrease in size in both the head and the abdomen 210. Available literature shows that gastroschisis infants are born with symmetric IUGR 202,208,209,211. This is unlike the findings from our present study, which show asymmetric IUGR with the infants’ HC being comparable to healthy preterm infants throughout the study period. This indicates normal brain growth for these infants.

Studies have also shown that prematurity and being SGA have been linked with poor neurodevelopmental and cognitive outcomes 212–214. On the other hand, other studies show that prematurity and/or SGA have modest to no effect on intellectual quotient and that other factors contribute to that 215,216. However, the studies that showed a link did not take into account the head size of the infants as a possible factor in the infants’ delayed neurodevelopmental outcomes, as it has been shown by some researchers that poor head growth was associated with intellectual
disabilities. Moreover, Hack et al. found that very-low-birth-weight (VLBW) infants with a subnormal head circumference had poorer cognitive function and academic achievement than VLBW infants without subnormal head circumference. From this, we can conclude that head size and growth—and not just the small size in these infants—play a major role in brain health and development. We also can conclude that the infants in this study might have improved neurodevelopmental outcomes because their head size was comparable to healthy preterm infants throughout the study period. Recent results from Minutillo et al. and Manen et al. support our findings on gastroschisis infants, mainly that those with simple gastroschisis have a promising and low incidence of adverse childhood neurodevelopmental outcomes.

It is valuable to note that the body weight and length for infants in this study continued to be low comparing to healthy infants at each measurement point through the study. Moreover, weight and length at the first PEA POD® were significantly lower than at birth, but the decrease was not statistically significant between the first and second PEA POD® measurements. This might indicate some catch-up in terms of weight and length gain through time, but we still cannot confirm or assess this, as more time and consecutive measurements were needed.

### 6.3 Body Composition Findings

BC data in this study was compared to BC data from a longitudinal study that was done on 160 exclusively breast-fed healthy infants from birth to 6 months of age using the ADP technique. In this study, we have shown that gastroschisis infants at term (first PEA POD® measurement) have significantly higher %FM, about the same FM, and significantly lower FFM when compared to healthy term infants for the same sex and age. These findings agree with previous data on preterm BC at term equivalent age that shows a higher %FM in preterms compared to healthy terms. Moreover, a recent systematic review and meta-analysis by Johnson et al. showed that preterm infants had greater %FM, less FM, and much less FFM than those born at full term. As we note, in our subjects and in other preterm infants in previous studies, FFM is always substantially lower. On the other hand, %FM is always higher, but the absolute FM is either lower or comparable to term infants. The higher percentage of fat in these infants may not be due to an increase in the fat content per se, but rather to very low FFM content, as was suggested by Johnson et al.
In the second PEA POD© measurement, when infants were approximately 2 months corrected age (47.4 corrected GA), they still showed a significantly lower FFM and a comparable absolute FM with reference infants for the same sex and age.

However, from the first PEA POD© measurement to the second, %FM and absolute FM had decreased significantly, but FFM was maintained when compared to reference. This trend might suggest a potential recovery or improvement for those infants over time. Due to the limited BC measurements we have done for these infants in this study, we cannot speculate the rate of catch-up or improvement for those infants or whether it will persist.

In their study using the same BC measurement method as in ours, Ramel et al. showed that preterm infants with lower FFM and higher adiposity at term had recovered at 3 to 4 months corrected age, with a non-statistically significant values of FFM and FM, when compared to term infants. Moreover, the FFM and FM for the first visit when their preterm infants reached term age were 2.97 kg and 0.68 kg, respectively. In our study, for the first measurement when our infants reached term age, FFM and FM were 2.50 kg and 0.44 kg, respectively. For the second visit, their infants showed FFM of 4.60 kg and FM of 1.81 kg. For our infants, it was 3.37 kg and 0.68 kg, respectively. Our infants show lower BC values in the first visit and even lower values for the second visit, compared to preterm infants in the study by Ramel et al. However, our infants were younger than theirs—approximately 2 months in the second visit. Between the first and second visits, their FFM gain was 1.63 kg, and the FM was 1.13 kg. In our infants, the gain was 0.87 kg and 0.24 kg, respectively. This shows a lower rate of gain in our infants. The regression noted here for our infants may be due to their younger age compared to the group studied by Ramel et al., plus the fact that ours are surgical sick neonates. As has been shown, the severity of illness is correlated with altered fat distribution and decreased FFM amounts in preterm infants.

In a randomized controlled trial by Roggero et al. that studied the effect of consuming nutrient-enriched formula for preterm infants on the gain in BC using ADP, we compared our group to the control group in this study who received standard formula. In their study, %FM at term was 14.5%, which is the same as our infants, and from 19.8% to 23% from 1 to 3 months, which is higher than our infants (16.9%) at 2 months corrected age. We could not compare with an exact value because their measurements were taken at 1 month and then at 3 months of corrected
age. Nevertheless, our infants show slower %FM gain than their infants. For FFM gain, it was 1.5 kg from term to 1 month in their infants, and 1.6 kg from term to 2 months in ours. However, their infants gained 1.3 kg from 1 to 3 months of corrected age. Thus, the FFM accretion seems to be higher in their group than our group.

BC data on sick infants are barely available. However, with the existence of the PEA POD© and its ease of use, more studies are being published on different groups of infants. A study on using the ADP technique to measure BC of neonates who received different major GI surgeries was published in 2015. It was interesting to compare findings of infants in our study to such a group, although they took BC measurements at just one point (at 43 weeks, corrected GA). The closest point to compare their infants to ours was with results from our first PEA POD© (at term). However, we could not do the comparison because of the three weeks’ difference in age between the two groups and because they just provided absolute BC values.

MUAC was comparable to that of healthy term infants at the two measurement points in this study. However, MUAC measurements alone reflect growth and nutritional status in general and do not differentiate between protein and energy stores in the body. It was more beneficial to measure triceps skinfold thickness in our infants in order to get a clearer indication of their arm muscle and arm fat sizes. Arm muscle size is calculated by subtracting triceps skinfold value from MUAC. The comparable MUAC in gastroschisis infants in this study might be due to their comparable fat stores with healthy term infants. However, infants in this study have shown a lower weight, but comparable MUAC to healthy infants. This finding might indicate a disturbed body composition distribution in gastroschisis infants in comparison to healthy infants. Moreover, this corresponds with our finding on the asymmetrical IUGR in those infants with a lower abdominal circumference.

In terms of nutrition for infants in this study, PN was generally started within the first 24 hours of life, depending on the gestation of the infant with gastroschisis. Generally, these infants are started on a higher amount of fluids (TFI of 120 ml/kg/d versus standard of 80 ml/kg/d) to make up for the increased fluid losses with the open defect. They proceeded according to the NICU nutrition guidelines of the hospital based on their gestation, and they likely have higher sodium requirements as well. Generally, no higher protein intake is required for infants with gastroschisis. However, the amount of protein given was dependent on the size of the defect and
if bowel resection was present. From this, we can note that these infants might need more protein than what they are already given.

Based on the aforementioned comparisons, we can conclude that infants in this study have significantly lower FFM and about the same FM when compared to healthy term infants. When compared to preterm groups, they are shown to have lower FFM and FM measurements than preterms. From this, we can deduce that FFM is the major deficit from which gastroschisis infants suffer, and that a reconsideration for their current nutritional management might be beneficial for this high-risk group. From my point of view, and based on the findings from this study, gastroschisis infants may be getting enough energy, unlike other preterm groups whom the studies have suggested are getting higher energy intakes based on their resulting high body fat content.

On the contrary, amino acids intake may still not be enough for this group of infants, and thus a recommendation for increasing their intakes should be considered as amino acids deficiency in preterm infants plays a role in impairing the development of growth, lean mass, bone, and brain. Moreover, it has recently been found that an increased amount of FFM gained early in life is associated with enhanced cognitive outcomes in preterms. Table 6-1 compares absolute BC data from other studies using the ADP technique with results from this study.
Table 6-1: Fat Mass and Fat Free Mass Data from other Studies in Infants Using the PEA POD© Compared to this Study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Term/Preterm</th>
<th>Age at Measurement (CGA(^1))</th>
<th>Health Status</th>
<th>FM(^2) (kg)</th>
<th>FFM(^3) (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This Study</td>
<td>12</td>
<td>Preterm</td>
<td>39.8 (1.4)</td>
<td>Gastrochisis</td>
<td>0.44 (0.2)</td>
<td>2.5 (0.3)</td>
</tr>
<tr>
<td>McLeod et al. (2015)(^199)</td>
<td>17</td>
<td>Preterm</td>
<td>39 (1.8)</td>
<td>Healthy</td>
<td>0.48 (0.2)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Roggero et al. (2010)(^229)</td>
<td>23 (girls)</td>
<td>Term</td>
<td>At birth</td>
<td>Healthy</td>
<td>0.26 (0.1)</td>
<td>2.71 (0.3)</td>
</tr>
<tr>
<td></td>
<td>17 (boys)</td>
<td></td>
<td></td>
<td></td>
<td>0.29 (0.09)</td>
<td>2.91 (0.2)</td>
</tr>
<tr>
<td>Carberry et al. (2010)(^230)</td>
<td>77</td>
<td>Term</td>
<td>At birth</td>
<td>Healthy</td>
<td>0.35 (0.1)</td>
<td>3.04 (0.3)</td>
</tr>
<tr>
<td>Cunto et al. (2015)(^225)</td>
<td>21</td>
<td>Preterm</td>
<td>43 (4)</td>
<td>Gastrointestinal surgery</td>
<td>0.52 (0.2)</td>
<td>2.99 (0.6)</td>
</tr>
<tr>
<td>Simon et al. (2014)(^231)</td>
<td>141</td>
<td>Preterm</td>
<td>37.3 (0.7)</td>
<td>Healthy</td>
<td>0.30 (0.1)</td>
<td>2.05 (0.2)</td>
</tr>
</tbody>
</table>

\(^1\)CGA: Corrected Gestational Age; \(^2\)FM: Fat Mass; \(^3\)FFM: Fat Free Mass. All data represented as mean (SD).
6.4 Maternal Findings

The inverse relationship between the prevalence of gastroschisis births and maternal age is the most consistently detected epidemiologic phenomenon of gastroschisis \(^{192}\). Studies have documented that teenager mothers < 20 years are more likely to have a gastroschisis infant than older mothers \(^{232-234}\). However, the mothers’ mean age in our study was 25.5 years, with 83% of them ≥ 20 years.

Moreover, a relationship between maternal BMI and gastroschisis has been also demonstrated. Undernourished mothers with low BMIs tend to be at higher risk of having an infant with gastroschisis \(^{235,236}\). Our study showed a different finding, with a mean maternal BMI of 26 kg/m\(^2\). Just one mother was classified as underweight, while the others were either normal, overweight, or obese. More studies are needed to investigate these new associations.

It also has been shown from the literature that infants born to overweight/obese mothers have higher FM than those born to lean mothers \(^{237,238}\). However, there was no data on maternal BMIs in the BC reference study to which we compared our infants, so we don’t know if they were lean or overweight. Moreover, our infants show comparable FM amounts with reference infants.

6.5 Limitations

The small sample size was a major limitation of the study. The sample size of 12 infants enrolled in the study depended on the number of gastroschisis cases admitted to the NICU of the Hospital for Sick Children. Successful recruitment of those infants further limited the sample size. There were some potential factors related to the unsuccessful recruitment, including that several infants were already participating in another research studies, the fact that results from this study did not directly or immediately affect participated infants like in interventional studies, and the absence of any kind of support in return for participation. All these factors played a role in limiting our sample size number. In addition, infants who were on ventilatory support, continuous infusions, or were critically ill were excluded as they could not fit in the PEA POD\(^{\circ}\).

The small sample size also affected the quality of statistical analysis used in the study, as this limited our ability to evaluate the effect of single contributing factors such as PN on BC. We were unable to perform a more sophisticated statistical analysis.
This was a single center study; all participants were from the Hospital for Sick Children. This might count as a limitation because population from this study may not be representative of general gastroschisis infants in Canada. Being a single center study also hindered us from having a matching control group for our infants other than a group found in the literature.

Moreover, since the study contained two points of BC measurements only, there was no long-term follow-up. Those infants might show a catch-up growth, especially since they were with simple gastroschisis. However, this study did not follow them enough to show such findings.

BC measurements at birth are missing in this study. The reason behind this limitation is that we could not perform PEA POD© measurement until after the surgery, when infants were medically stable. The time range for that was different between infants.

For the second PEA POD© measurement, we faced difficulty in having discharged infants return for their follow-up at the time we established (one month after the first measurement). Parents preferred to choose the follow-up time according to their convenience. Moreover, only 7 infants out of the 12-participating returned for the second PEA POD©. That was due to the long distance from where they live to the hospital for 3 infants, and the failure to get any response from the other 2. It might would have been more encouraging for the families to come back for follow-up if a reimbursement for time and travel was offered.

It would have been interesting to integrate other means of BC measurements in addition to the PEA POD©, such as triceps skinfold thickness or DXA, in order to compare results, test accuracies between methods, and to assess regional BC distribution in more details.

6.6 Strengths

This study was designed to address an area lacking in clinical research. The main strength of this study is that it measures the BC of gastroschisis infants for the first time. There were no previous studies that measured BC exclusively for gastroschisis infants. This study might also provide some idea of how surgical infants are doing in terms of BC.

This study also uses a unique and relatively new technique that has not yet been used as a routine measure in clinical care. We are one of only three hospitals in Canada with a PEA POD© device. Because of its non-invasive nature, the PEA POD© will allow for exploration of BC in different
high-risk group infants. This study will also serve as a base for future studies with larger sample sizes.

6.7 Implications

This study highlights the importance of measuring BC early in life, especially in high-risk infants who are more prone to adverse health outcomes during their lives. This work will encourage the assessment of BC in other groups of sick infants in the Hospital for Sick Children, as data in this area are scarce.

The current practice of depending on weight or BMI measurements to evaluate and assess preterm and sick infants’ growth is not enough. Exploring different BCs in different groups of infants at different stages will help in achieving accurate and more proper nutritional management and growth goals.

Moreover, with the availability of the PEA POD© device used in this study—an advanced, feasible, and easy-to-use BC technique, especially for high-risk, sick infants—the introduction of this practice in clinical settings will be easy, encouraging, and promising.

6.8 Future Work

We would recommend continuation of this work with a larger sample size and that infants be recruited from multiple centers to provide reference data for gastroschisis infants and other surgical populations. This would allow for broader population and would perhaps reduce the bias produced from being a single center study.

We also recommend more longitudinal studies on BC in sick infants by following them post-discharge and throughout their childhood. This will help in understanding the effect of the disease and the current management of FM and FFM in these infants, and the changes that occur over time. This would allow for clear decisions to be made regarding management and research.
Chapter 7
Conclusion

The present study advances the field by measuring the BC of a high-risk group of infants that was not measured previously.

In this study, we have shown that this group of high-risk infants is failing to gain weight at an appropriate rate. This appears to be due to failure to gain FFM. It is likely that the nutrition these infants receive while in the hospital plays a major role in this lean tissue deficit. More work is needed to adjust for this nutritional shortfall and to promote BC and overall growth in these infants.

We have also shown that the ADP technique is safe and feasible for measuring BC in this group of sick infants. We suggest that BC measurements should be continued to be evaluated as a routine part of growth monitoring, especially for sick and critically ill infants, as this will help in choosing the appropriate nutritional management. Future studies are needed to investigate interventions to promote lean mass gain in this population.


10. Sainz RD, Urlando A. Evaluation of a new pediatric air-displacement plethysmograph for


http://resolver.scholarsportal.info/resolve/08999007/v12i0001_s/45_dxaabc.


78. Lohman TG, Harris M, Teixeira PJ, Weiss L. Assessing Body Composition and Changes


98. Lozano A, Rosell J, Pallas-Areny R. Errors in prolonged electrical impedance
measurements due to electrode repositioning and postural changes. *Physiol Meas.* 1995;16(2):121.


158. Demerath EW, Guo SS, Chumlea WC, Towne B, Roche a F, Siervogel RM. Comparison


