Daily intake of yogurt drink fortified either with vitamin D alone or in combination with added calcium causes a thyroid-independent increase of resting metabolic rate in adults with type 2 diabetes: a randomized double blind clinical trial

Journal:	<i>Applied Physiology, Nutrition, and Metabolism</i>
Manuscript ID	apnm-2021-0248.R1
Manuscript Type:	Article
Date Submitted by the Author:	21-May-2021
Complete List of Authors:	Nikooyeh, Bahareh; National Nutrition and Food Technology Research Institute, Laboratory of Nutrition Research Shariatzadeh, Nastaran; National Nutrition and Food Technology Research Institute, Laboratory of Nutrition Research Rismanchi, Marjan; National Nutrition and Food Technology Research Institute Hollis, Bruce W.; Medical University of South Carolina, Department of Pediatrics Neyestani, Tirang; Shahid Beheshti University of Medical Sciences
Novelty bullets: points that summarize the key findings in the work:	Daily intake of vitamin D with calcium at physiological doses has attenuating effect on anti-TPO-Ab and TSH., Vitamin D with or without added calcium causes a thyroid-independent increase in RMR in euthyroid subjects with T2D.
Keyword:	Vitamin D, Calcium, Fortified yogurt drink, Type 2 diabetes, Resting metabolic rate, Randomized clinical trial
Is the invited manuscript for consideration in a Special Issue? :	Not applicable (regular submission)

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Daily intake of yogurt drink fortified either with vitamin D alone or in combination with added calcium causes a thyroid-independent increase of resting metabolic rate in adults with type 2 diabetes: a randomized double blind clinical trial

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Running title: Vitamin D, thyroid function and diabetes

Word count: 2'710 (excluding the abstract, references and tables)

Number of Tables: 3

Number of Figures: 0

Abstract

We investigated the effect of daily intake of yogurt drink fortified with either vitamin D alone or with added calcium on resting metabolic rate (RMR), thyroid hormones and homeostatic model assessment for insulin resistance (HOMA-IR) in subjects with type 2 diabetes (T2D). A total of 75 adult subjects with T2D were randomly assigned to one of the three groups to receive either D-fortified yogurt drink (DY; 1000 IU vitamin D/d), Ca-D-fortified yogurt drink (CDY; 1000 IU vitamin D plus 500 mg calcium), or plain yogurt drink (PY) for 12 weeks. All assessments were done at the baseline and after the intervention. The concentrations of anti-thyroid peroxidase antibody (anti-TPO-Ab), intact parathyroid hormone (iPTH) and thyroid stimulating hormone (TSH) had significant decline compared with baseline values only in CDY group. The mean RMR increased in both DY and CDY groups ($p < 0.001$ for both). Also, changes of serum concentrations of 25(OH)D ($B = 2.96$, 95%CI= 1.3- 4.6, $p = 0.001$) and iPTH ($B = -2.41$, 95%CI= -4.5- -0.31, $p = 0.025$) remained significant predictors of RMR changes even after adjustment for changes of serum concentrations of TSH ($B = -18.2$, 95%CI= -61.7- 25.2, $p = 0.406$). Daily intake of vitamin D together with calcium at physiological doses has attenuating effect on anti-TPO-Ab and TSH. Also, vitamin D with or without added calcium causes a significant thyroid-independent increase in RMR in euthyroid subjects with T2D.

Registered at clinicaltrials.gov as NCT01229891

Novelties

Daily intake of vitamin D with calcium at physiological doses has attenuating effect on anti-TPO-Ab and TSH.

Vitamin D with or without added calcium causes a thyroid-independent increase in RMR in euthyroid subjects with T2D.

Key words: Vitamin D; Calcium; Fortified yogurt drink; Type 2 diabetes; Resting metabolic rate

Draft

Introduction

Since the early works of Melanby and McCollum and discovery of vitamin D (DeLuca 2014), there seems to be still a lot to learn about this compound. Though the calcemic effects of vitamin D were recognized in the early 20th century, the list of the so-called non-calcemic effects is still being extended (Shirvani et al. 2019). One of the arguable non-calcemic functions of vitamin D is its role in energy metabolism and weight control (Fraser 2015; Soares et al. 2014). Identification of vitamin D receptors on adipocytes (Trayhurn et al. 2011), myocytes (Girgis et al. 2014) and other cells of the organs involved in energy balance (Fraser 2015) provided some evidence for the contribution of vitamin D in energy regulation. In adipose tissue, VDR expression is associated with systemic inflammation (Jonas and Kuryłowicz 2019), a common finding in obesity (Wilkins et al. 2018). The role of vitamin D in adipose tissue is intriguing. Some experimental studies reported vitamin D deficiency in adipose tissue of VDR knockout mice resulted in a resistance to diet-induced obesity (Bouillon et al. 2014), attenuation of hyperinsulinemia, accumulation of fat in liver (Liu et al. 2015) and increased energy expenditure (EE) as indicated by upregulation of uncoupling protein (UPC)-1, UPC-2 and UPC-3 in white adipose tissue (Narvaez et al. 2009; Wong et al. 2009). On the contrary, several human studies have reported a strong inverse relationship between circulating 25-hydroxycalciferol (25(OH)D) concentrations and body weight (Pourshahidi 2015; Zakharova et al. 2019). This association has been attributed to sequestration of vitamin D in adipose tissue as weight loss can actually improve vitamin D status in subjects with obesity (Pannu et al. 2016). Along the same line, some clinical trials reported significant reductions in body weight and waist circumference in the subjects supplemented with vitamin D (Nikooyeh et al. 2020a; Nikooyeh et al. 2016; Nikooyeh et al. 2011). Nevertheless, the effect of vitamin D on EE and body weight in humans is still controversial (Pathak et al. 2014).

One of the major regulators of EE and thermogenesis is thyroid hormones (Watanabe et al. 2006; Yavuz and Salgado Nunez Del Prado 2019). Hyperthyroidism induces increased EE which clinically presents as weight loss whereas hypothyroidism causes hypometabolic state and weight gain (Cicatiello et al. 2018). On the other hand, weight loss may be accompanied by alterations in serum concentrations of thyroid hormones in subjects with obesity (Marzullo et al. 2018). It is likely that leptin mediates signaling between adipose tissue and thyroid function (Reinehr 2010). Interestingly, several studies have documented a link between vitamin D and leptin (Kaneko et al. 2015). Association between vitamin D status and VDR with thyroid function and diseases has also been reported (Kim 2017; Muscogiuri et al. 2015; Wang et al. 2015). On the other hand, the relationship of thyroid hormones with insulin resistance (IR) and development of type 2 diabetes (T2D) has been documented (Lambadiari et al. 2011). Conversely, experimental evidence suggests an anti-diabetic function for thyroid hormones, notably T3, by enhancing insulin signaling and mitigating IR (Lin and Sun 2011). Even thyroid hormone mimetics have been proposed as an adjunct therapy for T2D (Baxter and Webb 2009). Though limited number of clinical trials have examined the effect of vitamin D supplementation on thyroid hormones and function (Cho and Chung 2020; Talaei et al. 2018), the possible relationship among vitamin D intake, thyroid hormones, EE and IR in the context of T2D has not been investigated to date. This study was, therefore, undertaken to examine the effect of daily intake of yogurt drink fortified with either vitamin D alone or calcium plus vitamin D on EE, thyroid hormones and IR in adult subjects with T2D. We used Persian yogurt drink (*doogh* in Persian) as a vehicle for fortification as it is a healthy popular dairy drink in Iran and can be easily consumed with each meal.

Materials and Methods

Study design

This was a randomized placebo-controlled clinical trial (registered at clinicaltrials.gov as NCT01229891), data and serum samples of which were available in our databank and biobank, respectively. By considering 80% of power, an effect size of 0.4 and by using the software G power 3.19.2 (Faul et al. 2007), a minimum sample size of 66 subjects was calculated. A total of 75 subjects (30 males and 45 females) were randomly selected from the databank. The participants were initially recruited from subjects registered at the Iranian Diabetes Society, as described elsewhere (Nikooyeh et al. 2011). Participants were adults aged 20-60 y with confirmed diagnosis of T2D. The exclusion criteria were pregnancy, lactation, regular intake of nutritional supplements since at least three months prior to the study, having any clinical disorders and taking any medications affecting vitamin D metabolism and/or thyroid hormones. The protocol and objectives of the study were fully described for all participants before they signed a written informed consent.

The subjects were randomly assigned to one of the three groups: (i) DY group who received 1000 IU vitamin D/d through consumption of two bottles of D-fortified yogurt drink (500 IU vitamin D and 150 mg calcium /bottle); (ii) CDY group who received 1000 IU vitamin D plus 500 mg calcium through consumption of Ca-D-fortified yogurt drink (500 IU vitamin D and 250 mg calcium/bottle); and (iii) PY group who received two bottles of plain (unfortified) yogurt drink a day (no detectable vitamin D and 150 mg naturally occurring calcium/bottle). We used vitamin D3 (DSM, Heerlen, Netherlands) and calcium citrate ($\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$, VWR Chemicals, Leuven, Belgium) to fortify the unflavored 1% fat yogurt drinks. Participants were instructed to drink two bottles of yogurt drink a day, preferably one with lunch and one with dinner for 12 weeks. The protocol and procedures of this study were

approved by the Ethics Committee of National Nutrition and Food Technology Research Institute (NNFTRI).

Dietary and anthropometric assessments

Assessment of dietary intake was done using an interviewer-led 24-h recall questionnaire for two days including one weekend. Weight and height were measured using a digital scale and stadiometer, respectively, to the nearest of 0.1 kg for weight and 0.1 cm for height. Body mass index (BMI) was calculated using the formula: $BMI = \text{weight (kg)} / \text{height}^2 \text{ (m)}$.

Laboratory investigations

Glycemic and vitamin D status

Serum samples were separated and kept at -80 °C, as described elsewhere (Neyestani et al. 2012; Nikooyeh et al. 2013; Nikooyeh et al. 2011). Concentration of fasting serum glucose was determined by an enzymatic method (Pars-Azmoon, Tehran, Iran) and using an auto-analyzer (Selecta E; Vitalab, Holliston, Netherlands). Serum insulin was measured by immunoradiometric assay (Biosource, Dorest, Belgium) and a gamma-counter system (Gamma I; Genesys). To evaluate insulin resistance (IR), homeostasis model assessment of insulin resistance (HOMA-IR) was applied, as reported previously (Nikooyeh et al. 2011).

To assess vitamin D status, serum 25(OH)D concentration was determined using high performance liquid chromatography (HPLC) (Neyestani et al. 2007). Our laboratory has been participating in the Vitamin D External Quality Assessment Scheme (DEQAS, www.DEQAS.org.uk) since 2012. Serum intact parathyroid hormone (iPTH) was determined by enzyme immunoassay (EIA) method and a commercial kit (Biomerica, USA), as described previously (Neyestani T.R. et al. 2015).

Thyroid function tests

Serum concentrations of thyroid stimulating hormone (TSH), free thyroxine (fT4; both from Pishtaz Teb, Tehran, Iran) and anti-thyroid peroxidase antibody (anti-TPO-Ab; Aeskulisa,

Wendelsheim, Germany) were assayed using EIA. All immunoassays were performed with the aid of a microplate reader system (Statfax 3200; Awareness Technology Inc., Palm City, FL, USA). Serum concentrations considered normal for TSH and fT4 were 0.32-5.2 mIU/L and 0.7-1.8 ng/dL, respectively. In this study, subjects with higher than normal levels of serum anti-TPO-Ab (<500 IU/mL) but normal TSH and fT4 concentrations were considered as euthyroid (Hutfless et al. 2011; Tipu et al. 2018).

Indirect calorimetry

To determine resting energy expenditure (RMR), indirect calorimetry (InCal) was employed using a calibrated respiratory gas analyzer (Fitmate pro, Cosmed, Rome, Italy) at room temperature ($25 \pm 2^{\circ}\text{C}$) while the participants was in supine position with a face mask and light clothing. The preconditions of InCal have been fully described elsewhere (Nikooyeh et al. 2020b). All measurements were done by a single device and staff under the same conditions, to minimize any possible variations. Total duration of the test was 15 minutes. Measurements with over 3 “non valid” data (more or less than 3 SD of mean for more than three minutes) were repeated on another day.

Statistical analyses

Continuous variables were expressed as the mean $\pm$ standard deviation (SD) or 95% confidence interval (CI), unless stated. Analysis of variance (ANOVA) (for variable with normal distribution) and Kruskal-Wallis test (for variables with non-normal distribution) were used for between-group comparisons at baseline and variable changes after intervention. Multivariate linear regression analysis was performed to explore the estimated effect of interventions on the outcomes of interests. Statistical significance was set at $p < 0.05$. All statistical analyses were done using Stata Statistical Software release 16 (Stata, College Station, TX, USA).

Results

Data were collected from 75 participants (mean age: 50.8 ± 5.8 years) of whom 44 were women (58.6%). Three groups were similar in terms of age ($p=0.501$) and gender ($p=0.513$) at baseline. Distribution of the studied variables did not show any significant between-group differences at the baseline (Table 1). Also, there were no significant within- or between-group differences in dietary intakes (Table 2).

Serum 25(OH)D concentration increased from baseline in both vitamin D-supplemented groups (DY: $+ 27.8 \pm 19.7$ and CDY: $+ 30.9 \pm 14.1$ nmol/L, $p < 0.001$ for both) and this was accompanied by a significant decrease in BMI in these two groups (DY: $- 0.6 \pm 0.13$ kg/m², $p < 0.001$; CDY: $- 0.35 \pm 0.12$ kg/m², $p = 0.009$).

All subjects were euthyroid. At the baseline, there was a strong correlation between anti-TPO-Ab and TSH concentrations ($r = 0.63$, $p < 0.001$). Serum TSH also expectedly showed an inverse correlation with fT4 ($r = -0.50$, $p = 0.001$). Interestingly, HOMA-IR well correlated with serum levels of anti-TPO-Ab ($r = 0.38$, $p = 0.004$) and TSH ($r = 0.28$, $p = 0.019$). Also, there was a negative but statistically insignificant correlation between HOMA-IR and circulating concentrations of fT4 ($r = -0.25$, $p = 0.063$).

After 12 weeks intervention, the concentrations of anti-TPO-Ab, iPTH and TSH had significant decline compared with baseline, only in the CDY group but not in DY or PY groups (Table 1). The observed decrease in serum iPTH ($p = 0.007$) and anti-TPO-Ab ($p = 0.005$) were significant compared with PY, as well. Interestingly, the mean RMR increased after 12 weeks intervention only in DY and CDY groups ($p < 0.001$ for both). Also, between-group comparisons showed that allocation to either group of vitamin D-supplemented groups, as compared with PY, had a significant effect on RMR at 12 weeks (DY $p = 0.023$ and CDY $p = 0.018$). We observed no significant within- or between-group

difference in serum fT4 concentrations in DY or CDY in comparison with PY group. Changes of serum 25(OH)D concentrations showed a negative correlation with both changes of anti-TPO-Ab ($r=-0.398$, $p=0.002$) and HOMA-IR ($r=-0.373$, $p=0.001$).

Table 3 displays the results of the regression models incorporating changes of serum 25(OH)D, iPTH and TSH concentrations with changes of RMR as the outcome. In univariate regression, changes of serum 25(OH)D ($B= 3.42$, $95\%CI= 1.88, 4.96$, $p<0.001$) and iPTH ($B= -3.43$, $95\%CI= -5.36, -1.49$, $p=0.001$) were the significant determinants of RMR changes. In multiple regression, changes of serum concentrations of 25(OH)D ($B= 2.96$, $95\%CI= 1.3- 4.6$, $p=0.001$) and iPTH ($B= -2.41$, $95\%CI= -4.5- -0.31$, $p=0.025$) remained significant predictors of RMR changes even after adjustment for changes of serum concentrations of TSH ($B= -18.2$, $95\%CI= -61.7- 25.2$, $p=0.406$) (Table 3).

Discussion

Our findings revealed an association of HOMA-IR with both anti-TPO-Ab and TSH supporting some previous reports (Vyakaranam et al. 2014). The relationship between IR and thyroid hormones has already been studied in both humans and animals (Martinez and Ortiz 2017). Serum concentrations of thyroxine (T4) close to the lower limit of normal range have been associated with increased IR in some studies (Kouidhi et al. 2013; Prats-Puig et al. 2012). However, in a study on one hundred healthy euthyroid adolescents from both sexes who were at high risk for developing T2D, HOMA-IR correlated with thyroid hormone T3, but not with TSH (de Jesús Garduño-García et al. 2015). Thyroid function influences glucose metabolism in many ways. It has been shown that thyroid hormones may have both insulin agonistic and antagonistic effects in muscles and liver, respectively (Brenta 2011). Therefore, any factor influencing on either glycemic status or thyroid hormones may also affect the other.

We found daily intake of just calcium-vitamin D-fortified yogurt drink for twelve weeks caused a significant decrease in anti-TPO-Ab and TSH in our subjects with T2D. The association between circulating 25(OH)D and thyroid hormone concentrations in the subjects with autoimmune thyroiditis (AIT) has been reported (Kivity et al. 2011; Koehler et al. 2019). It should be noted that none of our subjects had AIT and their thyroid test results were within normal ranges. Nevertheless, after 12 weeks intervention the increase in serum 25(OH)D concentrations was significantly associated with a decrease in anti-TPO-Ab. There are some reports of the suppressing effect of vitamin D on anti-thyroid antibodies and TSH (Aminian et al. 2019; Chahardoli et al. 2019; Villa et al. 2020). However, in those clinical trials much higher doses of vitamin D, i.e. 50000 IU weekly for 8-12 weeks, were used (Aminian et al. 2019; Chahardoli et al. 2019). This effect has been attributed to the immunomodulatory function of vitamin D (Gallo et al. 2019). Notwithstanding, this notion has been extensively argued (Vieira et al. 2020).

The inverse association between circulating concentrations of 25(OH)D and BMI has been repeatedly reported (Jorde et al. 2010; Pereira-Santos et al. 2015; Vimalaswaran et al. 2013). However, the relation between vitamin D and RMR has been less studied. We found that the intervention in both vitamin D supplemented groups, compared with control group, brought about a significant increase in RMR and also a significant decrease in BMI. Importantly, these changes were accompanied, but independent of, serum decline of anti-TPO-Ab and TSH. The effect of co-supplementation with low-dose vitamin D (400 IU) and high-dose calcium (1200 mg) for 15 weeks on fat mass loss just in female subjects with low habitual calcium intake has already been reported and this effect was attributed to reduced dietary fat intake due to calcium-induced appetite control (Major et al. 2009). However, we found no significant within- or between-group changes of dietary intake in our subjects. Notwithstanding, this effect may, at least in part, be due to dietary calcium-induced increased

fecal fat excretion (Christensen et al. 2009; Kjølbæk and Lorenzen 2017). On the other hand, the effect of vitamin D on RMR and body weight may be mediated through VDR (Sajjadi et al. 2018). Adequate intake of dairy calcium and vitamin D may help weight loss (Shahar et al. 2010) probably through, at least in part, increased EE. This effect on both EE and thyroid function is especially important in management of diabetes wherein weight control is crucial and thyroid dysfunction is relatively common (Biondi et al. 2019; Wilding 2014). Nevertheless, a meta-analysis failed to show any effect of vitamin D on body weight (Mora et al. 2013). One explanation for these discrepancies could be the initial calcium and vitamin D status of the subjects. Our participants had commonly low calcium and very low vitamin D intakes and consequently, as previously reported (Major et al. 2009), they might benefit more from Ca+D intervention. The effect of vitamin D on EE and weight control warrants further well-designed interventional studies.

Some limitations of this study are acknowledged. The observed effects of daily intake of yogurt drink fortified with either vitamin D alone or calcium plus vitamin D after 12 weeks can hardly be extended for longer durations. The effect of vitamin D and calcium on EE and thyroid function in subjects with both T2D and hypothyroidism needs further studies.

Conclusion

In the current study, we found that vitamin D together with calcium both at physiological doses has attenuating effect on anti-TPO-Ab and TSH in euthyroid subjects with T2D. Furthermore, vitamin D, with or without added calcium, caused a significant thyroid-independent increase in EE in our subjects. Considering the intrinsic link between thyroid function and insulin sensitivity (Fernández-Real et al. 2006), our finding of suppressing effect of vitamin D, with or without added calcium, on both anti-TPO-Ab and HOMA-IR and its

enhancing effect on EE implies the importance of a balanced nutrition providing sufficient amounts of calcium and vitamin D in diabetes.

Abbreviations

1	AIT: Autoimmune thyroiditis	15	HOMA-IR: Homeostasis model
2	ANOVA: Analysis of variance	16	assessment of insulin resistance
3	Anti-TPO-Ab: Anti-thyroid peroxidase	17	HPLC: High performance liquid
4	antibody	18	chromatography
5	BMI: Body mass index	19	iPTH: Intact parathyroid hormone
6	CDY: Calcium-vitamin D-fortified yogurt	20	IR: Insulin resistance
7	drink	21	25(OH)D: 25-hydroxycalciferol
8	CI: Confidence interval	22	PY: Plain (unfortified) yogurt drink
9	DEQAS: Vitamin D External Quality	23	RMR: Resting metabolic rate
10	Assessment Scheme	24	SD: Standard deviation
11	DY: Vitamin D-fortified yogurt drink	25	T2D: Type 2 diabetes
12	EE: Energy expenditure	26	TSH: Thyroid stimulating hormone
13	EIA: Enzyme immunoassay	27	UPC: Uncoupling protein
14	fT4: Free thyroxin	28	VDR: Vitamin D receptor

Conflict of interests

The authors report no conflict of interests in this study

Funding

Not applicable

Acknowledgement

All laboratory analyses were performed at the Laboratory of Nutrition Research, National Nutrition and Food Technology Research Institute. All yogurt drinks had been donated to the corresponding author by the Pegah Dairy Company, Tehran, Iran. We do appreciate the sincere collaboration of all participants.

Authors' contributions

This study was designed by TN with the intellectual aids of BN. Statistical analyses were done by BN. All laboratory bench works were done by NS, MR, BN and TN. Interpretation of findings was performed by TN, BN and BH. The preliminary manuscript was written by BN and revised and finalized by TN.

Draft

- Aminian, K., Bahrami, A., Najafipour, M., and Najafipour, F. 2019. Effect of vitamin D replacement on serum TSH in women with anti-TPO positive sub-clinical hypothyroidism. *J. Clin. Diagn. Res.* **13**(1). doi: 10.7860/JCDR/2019/38168.12426.
- Baxter, J.D., and Webb, P. 2009. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. *Nat. Rev. Drug Discov.* **8**(4): 308-320. doi: 10.1038/nrd2830.
- Biondi, B., Kahaly, G.J., and Robertson, R.P. 2019. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocrine Rev.* **40**(3): 789-824. doi: 10.1210/er.2018-00163
- Bouillon, R., Carmeliet, G., Lieben, L., Watanabe, M., Perino, A., Auwerx, J., et al. 2014. Vitamin D and energy homeostasis—of mice and men. *Nat. Rev. Endocrinol.* **10**(2): 79-87. doi:10.1038/nrendo.2013.226.
- Brenta, G. 2011. Why Can Insulin Resistance Be a Natural Consequence of Thyroid Dysfunction? *J. Thyroid Res.* **2011**: 152850. doi:10.4061/2011/152850.
- Chahardoli, R., Saboor-Yaraghi, A.-A., Amouzegar, A., Khalili, D., Vakili, A.Z., and Azizi, F. 2019. Can supplementation with vitamin D modify thyroid autoantibodies (Anti-TPO Ab, Anti-Tg Ab) and thyroid profile (T3, T4, TSH) in Hashimoto's thyroiditis? A double blind, Randomized clinical trial. *Hormone Metab. Res.* **51**(05): 296-301. doi: 10.1055/a-0856-1044.
- Cho, Y.Y., and Chung, Y.J. 2020. Vitamin D supplementation does not prevent the recurrence of Graves' disease. *Sci. Rep.* **10**(1): 1-7. doi: 10.1038/s41598-019-55107-9.
- Christensen, R., Lorenzen, J.K., Svith, C.R., Bartels, E.M., Melanson, E.L., Saris, W.H., et al. 2009. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. *Obes. Rev.* **10**(4): 475-486. doi:10.1111/j.1467-789X.2009.00599.x.
- Cicatiello, A.G., Di Girolamo, D., and Dentice, M. 2018. Metabolic effects of the intracellular regulation of thyroid hormone: old players, new concepts. *Front. Endocrinol.* **9**: 474. doi: 10.3389/fendo.2018.00474.
- de Jesús Garduño-García, J., Romero, E.C., Ochoa, A.L., Romero-Figueroa, S., Bravo, G.H., García, R.T., et al. 2015. Thyroid function is associated with insulin resistance markers in healthy adolescents with risk factors to develop diabetes. *Diabetol. Metab. Syndr.* **7**(1): 1-6. doi: 10.1186/s13098-015-0011-x. eCollection 2015.
- DeLuca, H.F. 2014. History of the discovery of vitamin D and its active metabolites. *BoneKEy Rep.* **3**. doi: 10.1038/bonekey.2013.213.
- Faul, F., Erdfelder, E., Lang, A.-G., and Buchner, A. 2007. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Method.* **39**(2): 175-191. doi: 10.3758/bf03193146.
- Fernández-Real, J.-M., López-Bermejo, A., Castro, A., Casamitjana, R., and Ricart, W. 2006. Thyroid Function Is Intrinsically Linked to Insulin Sensitivity and Endothelium-Dependent Vasodilation in Healthy Euthyroid Subjects. *J. Clin. Endocrinol. Metab.* **91**(9): 3337-3343. doi:10.1210/jc.2006-0841.
- Fraser, D.R. 2015. Vitamin D deficiency and energy metabolism. *Endocrinol.* **156**(6): 1933-1935. doi: 10.1210/en.2015-1298.
- Gallo, D., Mortara, L., Gariboldi, M.B., Cattaneo, S.A.M., Rosetti, S., Gentile, L., et al. 2020. Immunomodulatory effect of vitamin D and its potential role in the prevention and treatment of thyroid autoimmunity: a narrative review. *J. Endocrinol. Invest.* **43**(4): 413-429. doi:10.1007/s40618-019-01123-5.
- Girgis, C.M., Mokbel, N., Cha, K.M., Houweling, P.J., Abboud, M., Fraser, D.R., et al. 2014. The vitamin D receptor (VDR) is expressed in skeletal muscle of male mice and modulates 25-hydroxyvitamin D (25OHD) uptake in myofibers. *Endocrinol.* **155**(9): 3227-3237. doi: 10.1210/en.2014-1016.
- Hutfless, S., Matos, P., Talor, M.V., Caturegli, P., and Rose, N.R. 2011. Significance of prediagnostic thyroid antibodies in women with autoimmune thyroid disease. *J. Clin. Endocrinol. Metab.* **96**(9): E1466-E1471. doi: 10.1210/jc.2011-0228.
- Jonas, M.I., Kuryłowicz, A., Bartoszewicz, Z., Lisik, W., Jonas, M., Kozniowski, K., et al. 2019. Vitamin D Receptor Gene Expression in Adipose Tissue of Obese Individuals is Regulated by miRNA and Correlates with the Pro-Inflammatory Cytokine Level. *Int. J. Mol. Sci.* **20**(21). doi:10.3390/ijms20215272.

- Jorde, R., Sneve, M., Emaus, N., Figenschau, Y., and Grimnes, G. 2010. Cross-sectional and longitudinal relation between serum 25-hydroxyvitamin D and body mass index: the Tromsø study. *Eur. J. Nutr.* **49**(7): 401-407. doi:10.1007/s00394-010-0098-7.
- Kaneko, I., Sabir, M.S., Dussik, C.M., Whitfield, G.K., Karrys, A., Hsieh, J.C., et al. 2015. 1, 25-Dihydroxyvitamin D regulates expression of the tryptophan hydroxylase 2 and leptin genes: implication for behavioral influences of vitamin D. *FASEB J.* **29**(9): 4023-4035. doi: 10.1096/fj.14-269811.
- Kim, D. 2017. The Role of Vitamin D in Thyroid Diseases. *Int. J. Mol. Sci.* **18**(9). doi:10.3390/ijms18091949.
- Kivity, S., Agmon-Levin, N., Zisappl, M., Shapira, Y., Nagy, E.V., Dankó, K., et al. 2011. Vitamin D and autoimmune thyroid diseases. *Cell. Mol. Immunol.* **8**(3): 243-247. doi: 10.1038/cmi.2010.73.
- Kjølbaek, L., and Lorenzen, J.K. 2017. Calcium intake and the associations with faecal fat and energy excretion, and lipid profile in a free-living population. *J. Nutr. Sci.* **6**: e50. doi:10.1017/jns.2017.55.
- Koehler, V.F., Filmann, N., and Mann, W.A. 2019. Vitamin D status and thyroid autoantibodies in autoimmune thyroiditis. *Horm. Metab. Res.* **51**(12): 792-797. doi: 10.1055/a-1023-4181.
- Kouidhi, S., Berhouma, R., Ammar, M., Rouissi, K., Jarboui, S., Clerget-Froidevaux, M.-S., et al. 2013. Relationship of thyroid function with obesity and type 2 diabetes in euthyroid Tunisian subjects. *Endocr. Res.* **38**(1): 15-23. doi: 10.3109/07435800.2012.699987.
- Lambadiari, V., Mitrou, P., Maratou, E., Raptis, A.E., Tountas, N., Raptis, S.A., et al. 2011. Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes. *Endocrine* **39**(1): 28-32. doi: 10.1007/s12020-010-9408-3.
- Lin, Y., and Sun, Z. 2011. Thyroid hormone potentiates insulin signaling and attenuates hyperglycemia and insulin resistance in a mouse model of type 2 diabetes. *Brit. J. Pharmacol.* **162**(3): 597-610. doi: 10.1111/j.1476-5381.2010.01056.x.
- Liu, X.-J., Wang, B.-W., Zhang, C., Xia, M.-Z., Chen, Y.-H., Hu, C.-Q., et al. 2015. Vitamin D deficiency attenuates high-fat diet-induced hyperinsulinemia and hepatic lipid accumulation in male mice. *Endocrinology* **156**(6): 2103-2113. doi: 10.1210/en.2014-2037.
- Major, G.C., Alarie, F.P., Doré, J., and Tremblay, A. 2009. Calcium plus vitamin D supplementation and fat mass loss in female very low-calcium consumers: potential link with a calcium-specific appetite control. *Brit. J. Nutr.* **101**(5): 659-663. doi:10.1017/s0007114508030808.
- Martinez, B., and Ortiz, R.M. 2017. Thyroid Hormone Regulation and Insulin Resistance: Insights From Animals Naturally Adapted to Fasting. *Physiol. (Bethesda)* **32**(2): 141-151. doi:10.1152/physiol.00018.2016.
- Marzullo, P., Minocci, A., Mele, C., Fessehatsion, R., Tagliaferri, M., Pagano, L., et al. 2018. The relationship between resting energy expenditure and thyroid hormones in response to short-term weight loss in severe obesity. *PLoS One* **13**(10): e0205293. doi:10.1371/journal.pone.0205293.
- Mora, N., Rieke, K., Plitcha, J., Segura, A., Leehey, D., DeShong, K., et al. 2013. 25-Hydroxyvitamin D Supplementation and BMI Change: A Meta-Analysis of Randomized Controlled Trials. *J. Obes. Weight Loss Ther.* **3**(4): 181. doi:10.4172/2165-7904.1000181.
- Muscogiuri, G., Tirabassi, G., Bizzaro, G., Orio, F., Paschou, S.A., Vryonidou, A., et al. 2015. Vitamin D and thyroid disease: to D or not to D? *Eur. J. Clin. Nutr.* **69**(3): 291-296. doi:10.1038/ejcn.2014.265.
- Narvaez, C.J., Matthews, D., Broun, E., Chan, M., and Welsh, J. 2009. Lean phenotype and resistance to diet-induced obesity in vitamin D receptor knockout mice correlates with induction of uncoupling protein-1 in white adipose tissue. *Endocrinology* **150**(2): 651-661. doi: 10.1210/en.2008-1118.
- Neyestani T.R., Nikooyeh B, Kalayi A, Zahedirad M, and N., S. 2015. A vitamin D–calcium-fortified yogurt drink decreased serum PTH but did not affect osteocalcin in subjects with type 2 diabetes. *Int. J. Vitam. Nutr. Res.* **85**(1-2): 61-69. doi: 10.1024/0300-9831/a000227.
- Neyestani, T.R., Gharavi, A., and Kalayi, A. 2007. Determination of serum 25-hydroxy cholecalciferol using high-performance liquid chromatography: a reliable tool for assessment of vitamin D status. *Int. J. Vitam. Nutr. Res.* **77**(5): 341-346. doi:10.1024/0300-9831.77.5.341.
- Neyestani, T.R., Nikooyeh, B., Alavi-Majd, H., Shariatzadeh, N., Kalayi, A., Tayebinejad, N., et al. 2012. Improvement of vitamin D status via daily intake of fortified yogurt drink either with or without extra calcium ameliorates systemic inflammatory biomarkers, including adipokines, in the subjects with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **97**(6): 2005-2011. doi:10.1210/clinem.2011-3465.

- Nikooyeh, B., Zargaraan, A., Kalayi, A., Shariatzadeh, N., Zahedirad, M., Jamali, A., et al. 2020a. Vitamin D-fortified cooking oil is an effective way to improve vitamin D status: an institutional efficacy trial. *Eur. J. Nutr.* **59**(6): 2547-2555. doi:10.1007/s00394-019-02103-4.
- Nikooyeh, B., Neyestani, T.R., Tayebinejad, N., Alavi-Majd, H., Shariatzadeh, N., Kalayi, A., et al. 2014. Daily intake of vitamin D- or calcium-vitamin D-fortified Persian yogurt drink (doogh) attenuates diabetes-induced oxidative stress: evidence for antioxidative properties of vitamin D. *J. Hum. Nutr. Diet.* 27 Suppl 2:276-83. doi:10.1111/jhn.12142.
- Nikooyeh, B., Shariatzadeh, N., Kalayi, A., Zahedirad, M., and Neyestani, T.R. 2020b. Development of new predictive equations for basal metabolic rate in Iranian healthy adults: negligible effect of sex. *Int. J. Vitam. Nutr. Res.* 13: 1-10. doi:10.1024/0300-9831/a000669.
- Nikooyeh, B., Neyestani, T.R., Zahedirad, M., Mohammadi, M., Hosseini, S.H., Abdollahi, Z., et al. 2016. Vitamin D-fortified bread is as effective as supplement in improving vitamin D status: a randomized clinical trial. *J. Clin. Endocrinol. Metab.* **101**(6): 2511-2519. doi: 10.1210/jc.2016-1631.
- Nikooyeh, B., Neyestani, T.R., Farvid, M., Alavi-Majd, H., Houshiarrad, A., Kalayi, A., et al. 2011. Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. *Am. J. Clin. Nutr.* **93**(4): 764-771. doi:ajcn.110.007336.
- Pannu, P.K., Zhao, Y., and Soares, M.J. 2016. Reductions in body weight and percent fat mass increase the vitamin D status of obese subjects: a systematic review and metaregression analysis. *Nutr. Res.* **36**(3): 201-213. doi: 10.1016/j.nutres.2015.11.013.
- Pathak, K., Soares, M., Calton, E., Zhao, Y., and Hallett, J. 2014. Vitamin D supplementation and body weight status: a systematic review and meta-analysis of randomized controlled trials. *Obes. Rev.* **15**(6): 528-537. doi: 10.1111/obr.12162.
- Pereira-Santos, M., Costa, P.R.d.F., Assis, A.M.O.d., Santos, C.A.d.S.T., and Santos, D.B.d. 2015. Obesity and vitamin D deficiency: a systematic review and meta-analysis. *Obes. Rev.* **16**(4): 341-349. doi: 10.1111/obr.12239.
- Pourshahidi, L.K. 2015. Vitamin D and obesity: current perspectives and future directions. *Proc. Nutr. Soc.* **74**(2): 115-124. doi: 10.1017/S0029665114001578.
- Prats-Puig, A., Sitjar, C., Ribot, R., Calvo, M., Clausell-Pomés, N., Soler-Roca, M., et al. 2012. Relative Hypoadiponectinemia, Insulin Resistance, and Increased Visceral Fat in Euthyroid Prepubertal Girls With Low-Normal Serum Free Thyroxine. *Obesity* **20**(7): 1455-1461. doi: 10.1038/oby.2011.206.
- Reinehr, T. 2010. Obesity and thyroid function. *Mol. Cell. Endocrinol.* **316**(2): 165-171. doi: 10.1016/j.mce.2009.06.005.
- Sajjadi, S.F., Mirzaei, K., Khorrami-Nezhad, L., Maghbooli, Z., and Keshavarz, S.A. 2018. Vitamin D status and resting metabolic rate may modify through expression of vitamin D receptor and peroxisome proliferator-activated receptor gamma coactivator-1 alpha gene in overweight and obese adults. *Ann. Nutr. Metab.* **72**(1): 43-49. doi: 10.1159/000485662.
- Shahar, D.R., Schwarzfuchs, D., Fraser, D., Vardi, H., Thiery, J., Fiedler, G.M., et al. 2010. Dairy calcium intake, serum vitamin D, and successful weight loss. *Am. J. Clin. Nutr.* **92**(5): 1017-1022. doi:10.3945/ajcn.2010.29355.
- Shirvani, A., Kalajian, T.A., Song, A., and Holick, M.F. 2019. Disassociation of Vitamin D's calcemic Activity and non-calcemic Genomic Activity and individual Responsiveness: A Randomized controlled Double-Blind clinical trial. *Scien. Rep.* **9**(1): 1-12. doi: 10.1038/s41598-019-53864-1.
- Soares, M.J., Pathak, K., and Calton, E.K. 2014. Calcium and vitamin D in the regulation of energy balance: where do we stand? *Int. J. Mol. Sci.* **15**(3): 4938-4945. doi:10.3390/ijms15034938.
- Talaei, A., Ghorbani, F., and Asemi, Z. 2018. The effects of Vitamin D supplementation on thyroid function in hypothyroid patients: A randomized, double-blind, placebo-controlled trial. *Indian J. Endocrinol. Metab.* **22**(5): 584. doi: 10.4103/ijem.IJEM_603_17.
- Tipu, H.N., Ahmed, D., Bashir, M.M., and Asif, N. 2018. Significance of Testing Anti-Thyroid Autoantibodies in Patients with Deranged Thyroid Profile. *J. Thyroid Res.* **2018**: 9610497. doi:10.1155/2018/9610497.

- Trayhurn, P., O'Hara, A., and Bing, C. 2011. Interrogation of microarray datasets indicates that macrophage-secreted factors stimulate the expression of genes associated with vitamin D metabolism (VDR and CYP27B1) in human adipocytes. *Adipobiology* **3**: 31-36. doi: :10.14748/adipo.v3.269.
- Vieira, I.H., Rodrigues, D., and Paiva, I. 2020. Vitamin D and Autoimmune Thyroid Disease—Cause, Consequence, or a Vicious Cycle? *Nutrients* **12**(9): 2791. doi: 10.3390/nu12092791.
- Villa, A., Corsello, A., Cintoni, M., Papi, G., Pontecorvi, A., Corsello, S.M., et al. 2020. Effect of vitamin D supplementation on TSH levels in euthyroid subjects with autoimmune thyroiditis. *Endocrine* **70**(1): 85-91. doi: 10.1007/s12020-020-02274-9.
- Vimaleswaran, K.S., Berry, D.J., Lu, C., Tikkanen, E., Pilz, S., Hiraki, L.T., et al. 2013. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med* **10**(2): e1001383. doi: 10.1371/journal.pmed.1001383.
- Vyakarnam, S., Vanaparthi, S., Nori, S., Palarapu, S., and Bhongir, A.V. 2014. Study of Insulin Resistance in Subclinical Hypothyroidism. *Int. J. Health Sci. Res.* **4**(9): 147-153. PMID: 25580384.
- Wang, J., Lv, S., Chen, G., Gao, C., He, J., Zhong, H., et al. 2015. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. *Nutrients* **7**(4): 2485-2498. doi: 10.3390/nu7042485.
- Watanabe, M., Houten, S.M., Matak, C., Christoffolete, M.A., Kim, B.W., Sato, H., et al. 2006. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* **439**(7075): 484-489. doi:10.1038/nature04330.
- Wilding, J.P. 2014. The importance of weight management in type 2 diabetes mellitus. *Int. J. Clin. Pract.* **68**(6): 682-691. doi:10.1111/ijcp.12384.
- Wilkins, J., Ghosh, P., Vivar, J., Chakraborty, B., and Ghosh, S. 2018. Exploring the associations between systemic inflammation, obesity and healthy days: a health related quality of life (HRQOL) analysis of NHANES 2005–2008. *BMC Obes.* **5**(1): 1-12. doi: 10.1186/s40608-018-0196-2.
- Wong, K.E., Szeto, F.L., Zhang, W., Ye, H., Kong, J., Zhang, Z., et al. 2009. Involvement of the vitamin D receptor in energy metabolism: regulation of uncoupling proteins. *Am. J. Physiol. Endocrinol. Metab.* **296**(4): E820-E828. doi: 10.1152/ajpendo.90763.2008.
- Yavuz, S., and Salgado Nunez Del Prado, S. 2019. Thyroid Horm. Act. Energy Expend. **3**(7): 1345-1356. doi:10.1210/js.2018-00423.
- Zakharova, I., Klimov, L., Kuryaninova, V., Nikitina, I., Malyavskaya, S., Dolbnya, S., et al. 2019. Vitamin D Insufficiency in Overweight and Obese Children and Adolescents. *Front. Endocrinol.* **10**(103). doi:10.3389/fendo.2019.00103.

Table 1. Comparison of mean of variables in groups over time

Variables*	PY	DY	CDY	p value ¹	p value ³	p value ⁴	p value ⁵
BMI (kg/m²)							
Baseline	28.8±4.1	28.0±3.0	27.6±4.0	0.500	<0.001	0.031	0.211
Week 12	29.0±4.0	27.3±3.0	27.3±4.1				
p value ²	0.271	<0.001	0.009				
RMR (kcal/day)							
Baseline	1635.5±297.7	1557.2±302.2	1464.9±153.0	0.074	0.023	<0.001	0.018
Week 12	1575.4±296.5	1604.6±304.7	1623.6±154.0				
p value ²	0.057	0.106	<0.001				
25(OH)D (nmol/L)							
Baseline	32.9±18.1	41.9±18.9	36.1±21.4	0.261	<0.001	<0.001	0.780
Week 12	30.3±18.6	69.8±17.6	67.0±21.3				
p value	0.255	<0.001	<0.001				
PTH (pg/mL)							
Baseline	69.0±32.6	52.1±25.7	59.9±26.0	0.114	0.123	0.007	0.501
Week 12	75.7±24.0	48.8±20.2	51.0±23.8				
p value	0.073	0.350	0.008				
TSH (mIU/L)							
Baseline	2.22±1.29	2.26±1.21	2.20±1.57	0.984	0.978	0.283	0.352
Week 12	2.17±1.2	2.16±1.27	1.77±1.1				
p value	0.748	0.476	0.02				
ft4 (ng/dL)							
Baseline	1.61±0.22	1.62±0.2	1.73±0.4	0.400	0.489	0.158	0.704
Week 12	1.69±0.34	1.60±0.25	1.63±0.3				
p value	0.207	0.704	0.127				
Anti TPO-Ab (IU/mL)							
Baseline	135.1±134.6	138.2±101.5	138.4±103.9	0.995	0.662	0.005	0.036
Week 12	139.4±131.2	134.6±95.4	111.7±94.9				
p value	0.453	0.325	0.008				

*Mean variables at the baseline and after 12 weeks daily consumption of either plain, D-fortified or Ca+D-fortified yogurt drink.

¹ Between-group comparisons at baseline (one-way ANOVA), ² Within-group comparisons (Paired sample *t* test), ³ Post-hoc analysis of changes (DY vs. PY), ⁴ Post-hoc analysis of changes (CDY vs. PY), ⁵ Post-hoc analysis of changes (DY vs. CDY)

Anti TPO-Ab: anti-thyroid peroxidase antibodies; BMI: body mass index; CDY: Ca+D-fortified yogurt drink; DY: D-fortified yogurt drink; ft4: free thyroxine; 25(OH)D: 25-hydroxycalciferol; PY: plain yogurt drink; RMR: Resting metabolic rate; TSH, thyroid stimulating hormone

Table 2. Comparison of mean of variables of dietary intake in groups over time

Variables*	PY	DY	CDY	p value ¹	p value ³	p value ⁴	p value ⁵
Energy (kcal/day)							
Baseline	1534.3±499	1632.6±478.6	1534.8±491.6	0.700	0.977	0.872	0.758
Week 12	1525.0±409.6	1648.6±421.4	1463.7±367.2				
p value ²	0.930	0.839	0.355				
Protein (g/day)							
Baseline	62.8±24.5	59.9±19.9	56.2±22.9	0.770	0.370	0.415	0.998
Week 12	58.0±15.6	63.3±29.0	59.3±20.4				
p value ²	0.332	0.432	0.423				
Carbohydrate (g/day)							
Baseline	215.1±86.3	243.8±86.5	223.4±76.2	0.719	0.911	0.814	0.563
Week 12	203.6±58.0	241.0±89.6	198.6±58.4				
p value	0.473	0.864	0.06				
Fat (g/day)							
Baseline	49.3±18.7	49.0±15.5	49.8±26.1	0.279	0.789	0.793	0.388
Week 12	53.4±31.2	55.6±19.2	48.6±14.8				
p value	0.573	0.181	0.826				
Calcium (mg/day)							
Baseline	634.5±230.1	732.9±320.0	666.9±258.0	0.359	0.858	0.996	0.898
Week 12	664.3±242.1	738.2±310.0	689.6±279.1				
p value	0.575	0.936	0.677				
Vitamin D (IU/day)							
Baseline	26.4±15.7	18.5±11.4	22.2±19.0	0.183	0.399	0.999	0.389
Week 12	20.3±8.2	19.2±8.6	15.9±7.3				
p value	0.429	0.147	0.329				

*Mean variables at the baseline and after 12 weeks daily consumption of either plain, D-fortified or Ca+D-fortified yogurt drink. The extra amounts of the vitamin D and calcium intake due to fortification of yogurt drinks are not shown in this table.

¹ Between-group comparisons at baseline (one-way ANOVA), ² Within-group comparisons (Paired sample *t* test), ³ Post-hoc analysis of changes (DY vs. PY), ⁴ Post-hoc analysis of changes (CDY vs. PY), ⁵ Post-hoc analysis of changes (DY vs. CDY)

CDY: Ca-D-fortified yogurt drink; DY: D-fortified yogurt drink; PY: plain yogurt drink

Table 3. Multiple regression results for variables after intervention

Dependent variables	predictors	models	B	St. error	p value	95% CI	adjusted r ²
RMR changes	25(OH)D changes	crude	3.42	0.77	<0.001	1.88, 4.96	0.21
		Model ¹	2.78	0.79	0.001	1.19, 4.3	0.26
		Model ²	2.96	0.83	0.001	1.3, 4.6	0.27
	iPTH changes	crude	-3.43	0.97	0.001	-5.36, -1.49	0.15
		Model ¹	-2.28	0.96	0.020	-4.2, -0.37	0.26
		Model ²	-2.41	1.04	0.025	-4.5, -0.31	0.27
	TSH changes	crude	-24.9	24.8	0.319	-74.4, 24.5	0.014
		Model ²	-18.2	21.7	0.406	-61.7, 25.2	0.27

¹ variables in model 1: changes in serum 25(OH)D, changes in serum iPTH

² variables in model 2: changes in serum 25(OH)D, changes in serum iPTH, changes in serum TSH

25(OH)D: 25-hydroxycalciferol; iPTH: intact parathyroid hormone; RMR: resting metabolic rate; TSH: thyroid stimulating hormone