# TABLE OF CONTENTS

## Brief Report
1. Obesity and Antiphospholipid Syndrome: A Particular Challenge in Pregnancy  
   - Karoline Mayer-Pickel

## Research
2. Cardiovascular Risk Factors and their Responses to a 10 Weeks Training Program in Young Qatari Adults  
   - Zsuzsanna Kneffel, Ruben Goebel and Ahmad Alkhatib

## Research
3. Reward Deficiency Syndrome in Children: Obesity and Metabolic Disorders are Associated with the SNP TaqIA C32806T of the DRD2 Gene  
   - Renata M. Pinto, Daniela M. e Silva, Fabrício J. Queiroz, Fernanda R. Godoy, Lilian S. Teodoro, Isabella Lacerda, Marcos W. Gonçalves, Irene P. Pinto, Lysa Minasi, Thais C. Vieira and Aparecido D. da Cruz

## Research
4. Daily Calcium Intervention for a Weight-Loss Program Resulted in More Significant Decreases in Body Weight, BMI, Body Fat Mass, and Body Fat Percentage  
   - Yen-Ling Chen, Yi-Chun Chen, Jung-Su Chang, Jo Chun Lin and Yi-Wen Chien

## Mini Review
5. Post-Meal Exercise may Attenuate the Glycemic Response to a Carbohydrate Load: Important Implications for Adults who are Obese, with Pre-Diabetes or Diabetes, and/or At-Risk for Dementia  
   - Cynthia J. Heiss and Lynette R. Goldberg
Obesity and Antiphospholipid Syndrome: A Particular Challenge in Pregnancy

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ABSTRACT

Obesity is associated with a broad spectrum of chronic diseases, as well as cardiovascular diseases, such as diabetes, dyslipidemia, insulin resistance and hyperglycemia. Obesity during pregnancy is of major concern due to the well-known risk factors for both the mother and the child. Complications in pregnancy include recurrent miscarriages, gestational diabetes, hypertensive disorders, thromboembolism, and stillbirth. Additionally, maternal obesity seems to have long-term consequences for offspring, predisposing or "programming" them to the development of metabolic disease in adulthood. Antiphospholipid syndrome (APS) is an autoimmune disease and is characterized by the presence of antiphospholipid antibodies (anticardiolipin antibodies/ACLA, lupus antikoagulans/LA and β2-glycoprotein) in the maternal circulation. These antibodies are associated with arterial and/or venous thromboses and with adverse obstetric outcomes such as recurrent fetal loss, Preeclampsia (PE), Intrauterine growth restriction (IUGR) and Intrauterine fetal death (IUFD).

Obesity and APS are both chronic diseases with similar, even long-term consequences for mother and child; a co-occurrence of obesity and APS in pregnancy worsens the situation; the use of novel therapeutical tools should be therefore encouraged. A better understanding of the complex interactions between endothelial dysfunction and obesity and APS should be further investigated. Obese women with known APS should be counselled before conception not only about potential obstetrical complications as well as the long-term consequences for the off-spring, but also about these important life-style modifications. This review will provide an overview of obesity and APS in pregnancy and will discuss endothelial dysfunction as mechanism for adverse obstetric outcome in these chronic diseases.

KEYWORDS: Obesity; Pregnancy; Antiphospholipid syndrome; Endothelial dysfunction.

ABBREVIATIONS: APS: Antiphospholipid syndrome; PE: Preeclampsia; IUGR: Intrauterine growth restriction; IUFD: Intrauterine fetal death; BMI: Body Mass Index; RAAS: Renin-angiotensin-aldosteron system; APS: Antiphospholipid syndrome; SLE: Systemic Lupus Erythematoses; PAPS: Primary APS; NO: Nitric Oxide; ET-1: Endothelin-1; EDHF: Endothelium-derived hyperpolarizing factor; NOS: Nitric Oxide Synthase; ADMA: Asymmetric dimethylarginine; DDAH: Dimethylarginine dimethyl-aminohydrolase; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic.

INTRODUCTION

Obesity is a multifactorial chronic disease, which is characterized by an accumulation of fat in the body. Obesity has dramatically increased in both developed and developing countries in recent times. It is defined by the Body Mass Index (BMI). BMI is weight in kilograms divided by height in meters squared (kg/m²). Obesity is associated with a broad spectrum of chronic diseases, as well as cardiovascular diseases, such as diabetes, dyslipidemia, insulin resistance and hyperglycemia and degenerative joint disease, obstructive sleep apnea, gastroesophageal reflux, non-alcoholic fatty liver and certain types of cancer. It is a known fact that
obesity in pregnancy is increasing, rising from 3.2% in 1988 to 10.2% in 2002.9

Most of the comorbidities in obese patients can be explained by three “effects”:10 1) the “mechanical” effect with an accumulation of visceral fat, leading to an increase of intraabdominal pressure and i.e. activation of the Renin-angiotensin-aldosterone system (RAAS) with secondary hypertension, 2) the “metabolic effect” with peripheral insulin resistance and a systemic pro-inflammatory state and 3) the endothelial dysfunction with an imbalance of angiogenic factors. Endothelial dysfunction is known to be an early marker of atherosclerosis.10

This review will discuss obesity in pregnant women with Antiphospholipid Syndrome (APS) with focus on endothelial dysfunction as possible factor for adverse obstetric outcome in these women.

**OBESITY IN PREGNANCY**

Obesity during pregnancy is of major concern due to the well-known risk factors for both the mother and the child.

Pregnancy complications may arise from early gestation on, such as the increased risk of spontaneous, even recurrent abortions. Lashen, et al. described an odds ratio for miscarriages of 1.2 (95% CI 1.01 to 1.45) for obese pregnant women, additionally the authors revealed an increased risk for recurrent miscarriages.3,11 Unfortunately this increased risk has also been described in vitro fertilization therapy.13

Gestational Diabetes is a classical and not surprising consequence of obesity in pregnancy. Weiss, et al. demonstrated in a cohort of 16, 102 women, that the odds ratio for obese women to develop gestational diabetes is 2.6 (95% CI 2.1 to 3.4) and for morbidly obese women is 4.0 (95% CI 3.1 to 5.2).14

Another complication is the increased risk of macrosomia. The likelihood of delivering an infant weighing more than 4000 g was 1.7 times (95% CI 1.4 to 2.0) greater for obese and 2.0 times (95% CI 1.5 to 2.3) greater for morbidly obese women. The odds of delivering an infant weighing more than 4500 g was 2.0 times (95% CI 1.4 to 3.0) and 2.4 times (95% CI 1.5 to 3.8) greater for obese and morbidly obese patients, respectively.14

One important consequence of macrosomia is shoulder dystocia, a rare, but severe complication.15 Although fetal macrosomia is a risk factor for shoulder dystocia, the absolute risk of a severe shoulder dystocia associated with permanent impairment, or death, remains low.16 When the sensitivity and specificity of ultrasound to predict a birth weight >4500 g are included, it is estimated that 3695 non-diabetic women would require caesarean section to prevent a single case of permanent brachial plexus injury due to shoulder dystocia.15

It is a common fact that the rate of caesarean sections as mode of delivery is higher in obese women. Dietz, et al.17 analyzed 24, 423 nulliparous women stratified by pre-pregnancy BMI and pregnancy complications. The caesarean section rate was 14.3% for women with a BMI b19.8 kg/m2 and 42.6% for women with a BMI ≥35 kg/m2. This significant increase might be due to the fact that the first stage of labour is more often prolonged in obese women.

Another problem is the increased rate of especially postoperative complications in obese women, including blood loss >1000 ml, prolonged operative time, increased rate of postoperative wound infections and endometritis, and need for vertical skin incision.18,19

Postoperative infections are even increased in those obese women who have elective caesarean sections with prophylactic antibiotics.20

Hypertensive disorders in pregnancy might also be due to maternal obesity. Robinson et al. evaluated in their retrospective study over 15 years (1988-2002) an association of obesity and hypertensive disorders in pregnancy. The authors compared women whose weight was 55 to 75 kg with those whose weight was >90 kg. Compared with the normal weight group, the odds ratio of pregnancy induced hypertension for women with weight 90-120 kg (moderate obesity) was 2.38 (95% CI 2.24 to 2.52). The odds ratio for the group with women >120 kg (severe obesity) was 3.00 (95% CI 2.49 to 3.62).4 Severe forms of hypertensive disorders in pregnancy, such as preeclampsia and HELLP-Syndrome are also associated with obesity.

For the moderate obesity group the odds ratio of severe pregnancy induced hypertension, including HELLP syndrome, was 1.56 (95% CI 1.35 to 1.80) and for the severe obesity group was 2.34 (95% CI 1.59 to 3.46). These findings have been confirmed by others.14

Interestingly, the most prevalent risk factor for unexplained stillbirth is prepregnancy obesity.21,22 The mechanisms suggested for increased still-birth risk in the obese woman might be a decreased ability to perceive a reduction in fetal movement, as well as hyperlipidemia leading to atherosclerosis affecting placental blood flow, and increased snoring and sleep apnea associated with oxygen desaturation and hypoxia.23

In addition, epidemiological evidence and data derived from animal models have demonstrated that maternal obesity has long-term consequences for offspring, predisposing or “programming” them to the development of metabolic disease in adulthood.24 More and more literature demonstrates that the intrauterine environment is a predictor of future neonatal, child, and adult health.

Several studies describe an increased risk of obesity, diabetes mellitus and hypertension in the offspring.25-29 The risk of thromboembolism is not surprisingly increased in obese preg-
OBESITY RESEARCH

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OBESITY AND INFLAMMATION

In contrast to the “normal” inflammation, which has rather an acute character and is the response to injury or infection, the inflammation in obesity is chronic and is characterized by abnormal cytokine production, increased levels of adipokines such as CRP, IL-6, IL-18, TNFα, Angiotensin II, and leptin, as well as activation of inflammatory pathways. According to literature, maternal obesity is associated with metabolic inflammation, characterized by elevated adipose tissue and systemic proinflammatory cytokine levels and adipose tissue macrophage accumulation. These inflammatory processes are involved in vascular reactivity, thrombogenesis, angiogenesis, insulin sensitivity, and sympathetic nervous system. Additionally, these changes even affect the placenta, suggesting that maternal obesity exposes the fetus to an inflammatory environment during development. In animal models, maternal obesity has been shown to induce fetal inflammation which can result in promotion of adipogenesis and increased adiposity in offspring.

ANTIPHOSPHOLIPID SYNDROME (APS)

The antiphospholipid syndrome (APS) is an autoimmune disease, which is defined by clinical and laboratory criteria. APS occurs isolated as primary APS or combined with other autoimmune diseases, such as Systemic Lupus Erythematoses (SLE) or Raynaud disease.

The clinical manifestations might affect various organs and/or tissues; based on these manifestations one can divide between the thrombotic APS with the occurrence of arterial, venous or small-vessel thrombosis and the obstetric APS with a broad spectrum of pregnancy complications, including recurrent abortions, preeclampsia and placental insufficiency, with consecutive intrauterine growth restriction, as well as otherwise unexplained intrauterine fetal death.

The laboratory criteria are defined by the presence antiphospholipid antibodies (aPL) in the maternal circulation. Lupus coagulant is an immunoglobulin (usually IgG, IgM, or both) that binds to phospholipids and proteins associated with the cell membrane. Anti-cardiolipin anti bodies (ACLA) are acquired antibodies (IgG, IgM and/or IgA) that react against negatively charged cardiolipin. B2-Glycoprotein-1 (B2GP1) is present on the surface of trophoblastic cell membranes and has been added to the criteria in 2006. The presence of aPL is not only essential for the diagnosis of APS, it leads to the thrombotic and obstetric manifestations via various pathways. APL activate platelets and endothelial cells, inhibit fibrinolysis and interfere with the protein C pathway in patients with thrombotic APS.

Another mechanism for thrombosis has been reported to be an involvement of a defective function of Annexin V, a plasma protein, which has an antithrombotic character. In obstetric APS, aPL impair placentation, decreases thromboplast proliferation and invasion. Complement activation is essential for both thrombotic and obstetric APS. The complement system is suppressed in normal pregnancy. In pregnancies with APS, aPL bind to trophoblast cells and activate the complement system (C3a and C5a) with consecutive thrombosis and pregnancy loss. It has been suggested that local complement activation causes impaired thromboplast invasion and endothelial damage.

Another interesting approach is the theory that the inflammatory status in obese patients might induce antibodies-production itself. Gary, et al. demonstrated in a retrospective study that Primary APS (PAPS) occurs more often in obese patients. Fibrinogen-levels increased with BMI, suggesting that an elevated inflammatory state in overweight and obese patients might be a reason for the increased PAPS occurrence.

There are only a few authors who described obesity in APS-patients. Caldas, et al. compared obese and non-obese patients with primary APS. The obese PAPS-group had a higher frequency of adverse outcome as well as pulmonary embolism than the non-obese group. There was no difference in medication between the two groups.

ENDOTHELIAL DYSFUNCTION

The vascular endothelium is responsible for vascular function by producing vasoconstrictive and vasodilatating substances, which modulate vascular tone, activity of inflammatory cells and angiogenesis. The endothelium plays a pivotal role in vascular homeostasis, controlling the tone of blood vessels via the secretion of relaxing factors such as Nitric Oxide (NO), Prostacyclin (PG12) or Endothelium-derived hyperpolarizing factor (EDHF) and vasoconstrictive factors, including Angiotensin II, Endothelin-1 (ET-1), and thromboxane A2. An imbalance of all these factors leads to an endothelial dysfunction.

Nitric oxide (NO) is the main endothelium-derived relaxing factor, inflammation inhibitor, and suppressor of vascular smooth cell proliferation, platelet adhesion and tissue factor release. Therefore, it protects the vessels from atherosclerosis by an anti-inflammatory action, and inhibits the transformation of LDL, thrombus formation and smooth cell proliferation.

Endothelial Nitric Oxide Synthase (NOS) converts the amino acid L-arginine into L-citrulline and NO. Endothelial dysfunction is known to be the result of a decrease in NO, it is an impaired vascular reactivity; it also describes a pro-inflammatory and pro-thrombotic state and is known to be an early marker of atherosclerosis. Endothelial dysfunction results from endothelial cell injury and leads to endothelial cell activation.
and inflammatory process. There are many trigger factors leading to endothelial cell injury, i.e. hypoxia and turbulent blood flow. It has been described in many cardiovascular and metabolic disorders, such as arterial hypertension, coronary heart disease, peripheral vascular disease and diabetes mellitus I and II and preeclampsia.51-53

The bioavailability of NO can be altered by pathways, such as DDAH-ADMA-NOS pathway, oxidative stress or several factors, such as insulin. Insulin stimulates NO production by activation of NOS.54 Although insulin is vasodilatative,55-56 this effect might be altered in obese patients.57 However, insulin resistance is associated with a decreased NO bioavailability and impaired endothelial function.58-60

ASymmetric Dimethylarginine (ADMA)

Asymmetric dimethylarginine (ADMA) is an endogenous NOS inhibitor, which plays a key role in endothelial rearrangement. By decreasing NO-bioavailability, ADMA activates processes, which are involved in atherogenesis, plaque progression, and plaque rupture.61 A relationship of increased levels of ADMA and impaired endothelial function has been demonstrated. Associations of increased ADMA levels and high cardiovascular risk in hypertension, diabetes mellitus, insulin resistance, hypercholesterinemia, hypertriglyceridemia, hyperuricemia, obesity and hyperhomocysteinemia, as well as preeclampsia have been postulated.62-66

ADMA is eliminated via the urine or metabolized by the enzyme Dimethylarginine dimethyl-aminohydrolase (DDAH), by converting ADMA in L-citrulline and dimethylamine.67,68 Ito A, et al. have demonstrated that increased ADMA-levels in association with vascular disease and risk factors are mainly due to an decreased activity of DDAH.69

ADMA-levels are also elevated in obese patients, as well as in patients with metabolic syndrome. Hypercholesterinemia leads to a decrease of DDAH-activity with consecutive elevated ADMA-levels and endothelial dysfunction.70 Additionally, polymorphisms in the DDAH-1 and 2 genes have been associated with ADMA-levels in diabetes.71

In autoimmune diseases, such as APS and SLE, anti-endothelial cells antibodies including aPL lead to endothelial cell injury, apoptosis and endothelial dysfunction. Several studies have found higher levels of ADMA in patients with autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.72-75

Kiani, et al. showed in their study, that elevated ADMA-levels are associated with markers of poor prognosis in patients with SLE.76 Other authors proposed according to their results, higher ADMA- levels as independent risk factor for disease activity and poor prognosis.77,78

Several studies observed elevated ADMA concentrations in maternal circulation in women with preeclampsia.79-81 Savvidou, et al. reported that elevated ADMA-levels actually preceded preeclampsia, suggesting a possible preeclampsia screening parameter.82 ADMA concentrations increased at 23-25 weeks of gestations in women who developed late preeclampsia. The authors also found elevated titers of ADMA in pregnancies with pathologic uterine Doppler, including pregnancies with intrauterine growth restriction. These findings suggest a possible association with a pathologic placental perfusion.

Additionally ADMA serves as an antiangiogenic factor and high levels of ADMA affect negatively angiogenesis in pregnancy and preeclampsia.83 Di Simone, et al, found out that aPL are able to decrease endometrial endothelial cell angiogenesis. Beside complement activation, this mechanism might explain the defective placentation in pregnancies with adverse obstetric outcome in pregnancies with APS.84

ENDOTHELIN-1

ET-1, the most potent vasoconstrictor known;85 its overall action is to increase blood pressure and vascular tone. ET-1 acts by binding to two receptors: ETA and ETB, which are located on endothelial cells (ETB), vascular smooth muscle cells, and fibroblasts (ETA and ETB), both of them triggering vasoconstriction, cell proliferation, inflammation, and fibrosis.86 ET-1 decreases NO bioavailability, by decreasing NO production and by increasing NO degradation, thus leading to endothelial dysfunction.87

Amiri, et al. showed that the over-expression of ET-1 causes a decrease in NO and endothelial dysfunction.53 ET-1 is involved in endothelial dysfunction in several pathologic situations, such as atherosclerosis, diabetes mellitus and pulmonary arterial hypertension.87,95

Obesity is associated with vasoconstrictor tone, mediated by ET-1.96 A relationship of RAAS and ET-1 has been proposed.97 Activation of the RAAS increases angiotensin II, leading to an increased activity of endothelin converting enzymes and enhanced ET-1 expression.97

Normal pregnancy is associated with systemic vasodilation, decreased vascular contraction, resulting in a decrease of vascular resistance; partly due to increased release of endothelium-derived vasodilator substance, such as NO. Therefore reduced NO production/availability might lead to increased blood pressure and vascular resistance. The role of ET-1 receptor subtypes in the regulation of vascular function during pregnancy is unclear. A recent study found out, that the adaptive vasodilatation in pregnancy might be due to a down regulation of ET-1 receptors.98

ET-1 is also involved in the endothelial dysfunction in several autoimmune diseases.99-103 Several studies found elevat-
ed titers of ET-1 in patients with SLE.104,105 Ciółkiewicz, et al. found significantly increased concentrations of ET-1 in patients with active SLE.104 In another study the authors postulated a correlation between enhanced ET-1 levels and Lupus disease activity, measured by SLEDAI score.105

Atsumi, et al. found increased levels of ET-1 in patients with arterial thrombosis, but not in venous thrombosis, suggesting that ET-1 induced by antiphospholipid antibodies might play an important role in altering arterial tone, leading even to occlusion.106

Other authors did not find increased ET-1 concentrations in patients with APS.107,108 Williams, et al. presumed that one reason might be the anti-inflammatory effect of the patient’s medication, such as salicylates.

Multiple studies have found elevated levels of ET-1 in women with preeclampsia, some of these studies indicate that the level of circulating ET-1 correlates with the severity of the disease symptoms.109-111 However, ET-1 serves as a marker for endothelial dysfunction in preeclampsia, but also as predictor in women who develop preeclampsia.109-111

MANAGEMENT

A prepregnancy weight loss should be the first and simplest way for a better maternal and neonatal outcome. A recent study demonstrated that even small differences in prepregnancy BMI (10%) are associated with less than a 10% lower risk of preeclampsia, gestational diabetes, indicated preterm delivery, macrosomia, and stillbirth. In contrast, larger differences in prepregnancy BMI (20-30% differences in BMI) were necessary for significant reduced risks of cesarean delivery, shoulder dystocia, neonatal intensive care unit stay 48 hours or longer, and in-hospital newborn mortality.112,113 Unfortunately, many patients tend to maintain prepregnancy lifestyle habits throughout pregnancy; To reduce adverse obstetric outcome and negative long-term complications, especially in the off-spring, certain nutritional interventions as anti-inflammatory strategy, such as Eicosapentaeonic Acid (EPA) and Docosahexaenoic (DHA), Taurine and Curcumin are another important possibility. These dietary interventions are particularly to minimize complications in the fetal/neonatal development.114 Bariatric surgery is the most appropriate strategy to lose weight when others fail.110

The basic treatment of APS in pregnancy is low-dose aspirin and low-molecular-weight-heparin. The efficacy of corticosteroids remains uncertain; its use is discouraged solely for the treatment of APS.

Alijotas, et al. formed the term “refractory obstetric antiphospholipid syndrome” and described several treatment options for cases with adverse obstetric outcome despite therapy, which consisted i.e. of intravenous-immunoglobulins (IVIG), corticosteroids, antimalarias, TNF-targeted therapies or other immunomodulatory agents such as pentoxifylline.115

Heparin has a variety of actions including anticoagulant activity and inhibitory actions on vascular smooth muscle cell proliferation and migration, as well as anti-inflammatory effects.116-118 It is also known that heparin acts as an endogenous antiatherosclerotic factor,118-120 and chronic use of heparin shows a blood pressure-lowering effect in hypertensive patients and experimental animals.121,122 In endothelial cells, ET-1 has been shown to be suppressed by heparin in cultured bovine endothelial cells.123-125 Kuwahara-Watanabe, et al. demonstrated in their study that heparin suppressed ET-1 gene expression at the transcription level.126

ET-1 is responsible for endothelial dysfunction; therefore it serves as a possible therapeutic target in several diseases.127 ET receptor antagonists as treatment for preeclampsia has also been discussed several studies.127-130 Generally, the treatment with all endothelin receptor antagonists, such as sitaxsentan, ambisentan, atrasentan is contraindicated in pregnancy because the use of ETA receptor antagonists during pregnancy has proven to cause birth defects and embryonic lethality in mice.131,132 ETA receptor antagonists might be used in later pregnancy134,135 for treatment of preeclampsia.

Tumor-necrosis-factor-alpha (TNF-alpha) is known to be jointly responsible for aPL-related placental injury and consecutive miscarriage. Anti-TNF-alpha drugs, such as infliximab, etanercept and adalimumab are used for the treatment of certain rheumatic, digestive and cutaneous immune-mediated diseases. Anti-TNF-agents are also thought being used in cases of so-called “refractory obstetric APS”.133 Its use during pregnancy has been reported being safe, although anti-TNF drugs are still classified by the FDA as ‘pregnancy risk category B’.115

According to literature tumor-necrosis-factor inhibits enzymatic degradation of ADMA; therefore anti-TNF agents could restore physiological level of ADMA. Spinelli, et al. treated 33 patients with rheumatoid arthritis for 3 months either with etanercept or with adalimumab. They demonstrated a significant decrease of ADMA-levels.136 Therefore, anti-TNF-drugs as possible treatment for cases of especially refractory obstetric antiphospholipid syndrome should be further investigated.

CONCLUSION

Obesity and antiphospholipid syndrome (APS) are both chronic diseases with similar, even long-term consequences for mother and child. Both diseases are associated with adverse obstetric outcome; a co-occurrence of obesity and APS in pregnancy worsens the situation; the use of novel therapeutic tools should be therefore encouraged. The NO-pathway and inflammation are among the key mechanisms likely involved in the endothelial dysfunction in both conditions. A better understanding of the complex interactions between endothelial dysfunction and obesity and APS should be further investigated. Goals of treat-
ment in obesity and APS in pregnancy are to improve the maternal and fetal/neonatal outcome. However, pre-pregnancy weight loss, as well as changes in life-style are feasible methods, which might prevent or delay the onset of endothelial dysfunction; therefore obese women with known APS should be counselled before conception not only about potential obstetrical complications as well as the long-term consequences for the off-spring, but also about these important life-style modifications.

CONFLICTS OF INTEREST

The author declares that this article content has no conflicts of interest.

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Cardiovascular Risk Factors and their Responses to a 10 Weeks Training Program in Young Qatari Adults

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ABSTRACT

Rapid development in Qatar in recent years has led to numerous changes, particularly the increased prevalence of lifestyle related health risks, with almost 50% obesity rates amongst Qatari of all ages. We investigated the effects of a 10-week exercise training program aimed at young Qatari adults, on a number of Cardiovascular disease (CVD) risk factors. With Qatar University IRB approval, we screened 158 (89 males, 69 females) Qatari student volunteers for CVD factors of hypertension indicated by Systolic Blood Pressure (BPS) and Diastolic Blood Pressure (BPD), overweight and obesity indicated by Body Fat percentage (%BF), Body Weight (BW) and Body Mass Index (BMI). Thirty six participants (23% of total number) were identified with one or more risk factors (hypertension and overweight), and were enrolled to follow a 10-week recreational-type exercise training program. The training involved 30-45 min of either walking, cycling, jogging and swimming at an exercise intensity corresponding to 50-85% of each participant’s maximum heart rate, on 3-5 times/week. The intervention significantly reduced BW (93.4±14.1 vs. 86.7±14.5, and p<0.05), BMI (31.0±3.6 vs. 28.7±3.9, p<0.05) and BF% (31.2±9.0 vs. 21.2±4.4, p<0.05) in males, and there was a significant reduction in BPD (83.4±5.3 vs. 76.0±9.2 mm Hg, p<0.05). The effects in female participants were not significant. This recreational-type exercise intervention was effective in substantially reducing the CVD indices. However, the alarmingly high prevalence of sedentary-related CVD risks amongst Qatari young adults, especially those related to obesity, overweight and hypertension necessitate further public health interventions in this age-group as an early prevention strategy.

KEYWORD: Physical Activity; Health risks; Interventions; University workplace.


INTRODUCTION

Exercise is an established primary and secondary prevention strategy in a variety of populations of all ages, including sedentary and those at high CVD risks.1-4 Multipronged interventions, particularly the exercise-based, in young people have been suggested as an effective preventative approach in identifying and reducing various CVD risks at an early stage and have shown various degrees of effectiveness.5,6

The university campus workplace serves as a unique and ideal setting for health promotion mainly because of its exposure of many healthy massages to a large number of young adult students and staff.7 Effective health screening and exercise interventions within a university campus have been shown to increase the awareness of existing sedentary lifestyle risks such as elevated blood glucose, body fat percentage and blood pressure, and reduced cardiorespira-
Qatari population has received very little attention in terms of obesity research despite the country recording the highest obesity and physical inactivity rates across the WHO-classified regions, perhaps due to recent emergence of wealth and natural resources in the GCC region, which has impacted on its populations’ health and lifestyle. Limited data available have indicated that over 41% of its population being physically inactive, 76% of its male adults being classified as overweight or obese reflecting the highest percentage among the GCC and Western countries, whilst, hypertension rates are also high and over 32% of Qatari adults. This obesity and physical inactivity prevalence was coupled with a dramatic increase in the prevalence and incidence of non-communicable diseases, particularly over the past 20 years. The prevalence of cardiovascular diseases (CVD), account for significant levels of mortality (30.2%) in Qatar, which is comparable with the highest recorded rates in the United States and European Union, of 30.4% and 40% respectively. Therefore, effective interventions are very much needed amongst Qatari populations.

To date there are no studies on the CVD prevalence amongst Qatari young adults, especially given that half of Qataris (n=278,000) are under 20 years. Despite some earlier CVD prevalence studies amongst Qatari and non-Qatari living in Qatar, neither screening nor efficacy of a physical intervention have been investigated.

Therefore, the aim of the study was to assess the prevalence of lifestyle disease risk factors amongst young Qatari adults students. A second aim is to test the effectiveness of a 10-week exercise-training program aimed at young Qatari adults, on a number of cardiovascular risk factors. We hypothesize that a university based intervention could reduce the CVD risk actors amongst young Qatari students.

METHODS

Participants and Design

All participants were students within Qatar University, Doha. The study was reviewed and approved by the Institutional Review Board (IRB) for Human Subjects. All of the undergraduate Qatari students at the university received invitation e-mails to take part in the study (ca. 1300). In addition, leaflets and posters were distributed around the university campus. One hundred and fifty eight students (n=158, 89 males and 69 females) with the age of 18-30 years old, expressed interest to volunteer in the study and provided a written informed consent prior to participation in this study. The eligibility criteria used included: 1) no previous diagnosed health or current medication (anti-hypertensive medication and/or anti-depressive treatment), 2) ability to attend the whole duration of the intervention and 3) proved Qatari citizenship.

Initial Screening and Testing Procedures

The testing adhered to the Helsinki declaration for the use of human subjects. All participants were individually interviewed and assisted in filling the short form of the International Physical Activity Questionnaire (IPAQ). Body weight (BW) was assessed to the nearest 0.1 kg (Omron BF-400, Healthcare Co., Ltd., Japan), and Body Height (BH) was assessed to the nearest 0.5 cm. Systolic (BPS) and diastolic (BPD) blood pressure were assessed resting (sitting position) for 5 minutes using digital monitor (Omron HEM-780, Omron Healthcare Co., Ltd., Japan) and recorded twice with 1-minute break in between, and the taken value was within 10 mm Hg. Body composition was assessed for body fat percentage (%BF) using a single frequency bioelectrical impedance analyzer at 50 kHz (Omron BF-400, Healthcare Co., Ltd., Japan), and recorded twice with 1-minute break in between, and was calculated as weight/height² (kg/m²). Exercise Intervention

After the screening process, 36 participants (23% of total number) who were identified with one or more risk factors (elevated blood pressure or overweight) were enrolled to follow a 10-week recreational-type exercise training program. Eight students reported that they could not complete the intervention due to different reasons (e.g. injury, time conflict), and a further three dropped out during the intervention. Two female students dropped out because of pregnancy. At the end of the intervention overall 23 participants (13 males and 10 females) have completed the whole intervention and their results were analyzed.

The 10 weeks exercise training intervention involved either walking, cycling, jogging and swimming at an exercise intensity corresponding to 50-85% of each participant’s maximum heart rate, (monitored by POLAR FT4, in every 2 minutes), lasting 30-45 min, five times per week. The first three training sessions were in the form of supervised training, whilst the participants performed the remaining two sessions individually after they were all given a training schedule. This training regime was similar to a previously recommended PA protocol for this age group and according to the recommendations of the American Heart Association. All training sessions were conducted at Qatar University’s facility of the gymnasium and the outdoor track.
Data Analysis and Statistics

All screened cardiovascular risks (BPS, BPD, BMI, %BF) were reported as mean ± standard deviation. The results of each risk factor were compared against the recommended value based on WHO classifications. The Physical Activity (PA) levels were categorized into Walking (W), Moderate intensity activities (M), Vigorous-intensity activities (V) according to the number of hours reported and applied the recommended MET by IPAQ-short guidelines. To determine the effects of the used intervention and compare the pre- and post- assessments, self-control trials (paired t-test) were used. Data were analyzed using SPSS, version 21.0 and the significance level was set at p<.05.

RESULTS

Initial Screening Results

Both males and females have demonstrated a high prevalence in the risk factors of BMI, %BF and BPS above the recommended thresholds (BPS>120 mm Hg, BMI>25, %BF>18.9), (Table 1). For males, BPD was within the normal range (BPD<80 mm Hg) and nineteen participants (21.3%) had elevated blood pressure and exceeded the recommended thresholds, (Table 1). Twenty-eight (31.5%) of the participants were classified overweight and similarly 31.5% were obese by BMI. Additionally, %BF shown that twenty-two (24.7%) were overweight and twenty-seven (30.3%) were obese;

The total PA for males was (424.18 MET-minutes per week), which was below the recommended 500-1000 MET-minutes per week. The resulting classifications were as follows: the vigorous PA, 267.48 MET min/week, walking PA, 89.52 MET min/week and moderate PA, 67.18 MET min/week.

In terms of the female participants’ data, thirteen (18.8%) were classified overweight and seven (10.1%) were obese by BMI. Additionally, %BF shown that sixteen (23.2%) were overweight and twelve (17.4%) were obese; ten (14.5%) had elevated blood pressure above the recommended thresholds (Table 1).

Females’ total PA (462.37 MET-minutes per week) was also below the recommended 500-1000 MET-minutes per week. The resulting classifications were as follows: the vigorous PA, 127.36 MET min/week, walking PA, 264.94 MET min/week and moderate PA, 62.51 MET min/week.

Intervention results

The intervention significantly reduced BW, BMI and %BF (all p<0.05), (Table 1). BPD was significantly reduced (83.4±5.3 mm Hg vs. 76.0±9.2 mm Hg, p<0.05), but not BPS (133.81±10.7 mm Hg vs. 130.5±9.1 mm Hg, p=0.52). Average BMI overweight and obesity percentages were significantly reduced among the participants (Table 1).

DISCUSSION

The study aimed to demonstrate the prevalence of cardiovascular risk factors and the efficacy of a 10-week physical activity intervention within a cohort of Qatari students with defined risk factors. Two main findings are that young Qatari adults in this setting demonstrate high prevalence of CVD risks, which is slightly higher than what is reported nationally for all Qatari adults. The second main finding of the present study is that the intervention significantly reduced BW, BMI and %BF (Table 1).

Our results have shown that prevalence of overweight and obesity among this sample (each 31.5%) is similar to what have been reported among adolescent in seven Arab Countries including Qatar. Comparing the initial screening results of BMI

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Initial data</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
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<td>69</td>
<td>13</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>BPS (mm Hg)</td>
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<td>115.4±10.6</td>
<td>.05</td>
</tr>
<tr>
<td>BPD (mm Hg)</td>
<td>74.4±11.6</td>
<td>74.2±9.1</td>
<td>.21</td>
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<tr>
<td>BW (kg)</td>
<td>82.4±19.7</td>
<td>60.5±15.0</td>
<td>.03</td>
</tr>
<tr>
<td>BMI</td>
<td>27.3±6.2*</td>
<td>23.2±5.6</td>
<td>.15</td>
</tr>
<tr>
<td>BF (%)</td>
<td>22.9±10.3*</td>
<td>29.6±10.5</td>
<td>.32</td>
</tr>
</tbody>
</table>

BPS: systolic blood pressure; BPD: diastolic blood pressure; BW: body weight; BF: percentage of body fat; BMI: body mass index.

Table 1: Means±SD for all assessments indicating cardiovascular risk factors.
to age matched results of two Western countries, we found that the percentage of obesity (Table 1) was close as data among Americans,29 33.2% and was markedly higher than obesity data in the UK,30 32.6%. The overweight prevalence of 31.5% in our study was close to that 33% which was reported in an earlier research of older Qatari population16 and higher than it was reported for a younger Qatari adolescent cohort18 of 28.6%. These results could demonstrate a rising tendency of bodyweight as a marked CVD risk factor in young Qatari adults. The prevalence of overweight and obesity indicated by BMI≥25 of 63% in our study is similar to the 65% reported in earlier research for Qatari males when matched age in Qatar.15 This alarming rate not only supports the global concern of rising obesity globally,28 but is also a major concern for developing CVD, particularly diabetes at early adulthood in the GCC region.31

The intervention was effective in reducing obesity and overweight related measures. If those are distributed across the overall sample, it will equate to a 7.4%, 7.2% and 5.4% reduction in the average of BMI, BW, and %BF respectively (Table 1). This reduction rate is similar to what is found in other interventions with a similar period of time an 8 week long study, that applied an aerobic training program.32 Those authors described a moderate physical activity promoted decrease in BMI (28.1±1.59 vs. 25.7±0.75, p<0.05) and body fat distribution (31.8±3.7 vs. 28.6±2.6, p<0.05) among obese, and enhanced their pulmonary indices (FVC, FEV1), VO2max.33 The transition from adolescence to young adulthood is a critical period for obesity development with one study noting that obesity rates doubled from adolescence to the early twenties,33 and another reporting that there is both a high incidence and maintenance of obesity from adolescence to early adulthood.34 Therefore, this study contributes in addressing the measured risk factors in these young age-groups.

The initial screening revealed over 20% of BPS in both young males and females indicating pre-hypertension risks (BPS>120 mm Hg) in those participants, and a major risk factor for CVD.35 Even though the mean reductions was significant after the 10-weeks of training program in three variables (BPS, BMI, %BF), there was still individual cases of pre-hypertension, and those individuals were referred to see their physician in order to continue being supervised following the intervention. In those where the initial BPS was ≥130 mm Hg, the training program used resulted in significant reduction and the average decrease was 7 mm Hg (p<0.05), however in participants where the initial value was <130 mm Hg the mean reduction was only 1.1 mm Hg (p=0.4). These results are quite similar to those experienced in some longer 6-month-long longitudinal studies in which the decrease of the BP depended on the initial values. When it was high, the decrease was more marked,36,37 but in normotensive subjects it was only 3-4 mm Hg.38,39

According to a previous observation40 the best age to produce a beneficial effect on BP is between 30 and 49 years. In the present study participants’ mean age was 20 years. suggesting that the training effects on BP at this age could be less marked than in older participants.5

Failure to meet physical activity guidelines amongst university students has been reported as a reason for weight gain, especially amongst freshman year students41,42 (five days of moderate activity for 30 min, or three days of vigorous activity for 20 min).3,44 It is perhaps important to note that the student cohort we tested had the option to sit on one of the sport courses that were offered within the curriculum, and had the option to use the campus-based sport facilities. However, the effectiveness of these approaches still appears inadequate for weight maintenance.5 Our results appear to agree that integrating PA within the university curriculum does not necessarily reflect in meeting the PA levels amongst university students.

It is well established that exercise is a primary prevention for CVD and several exercise intervention studies have shown exercise training effectiveness in a number of cardiovascular and metabolic indices including reducing blood pressure and indices of the metabolic syndrome.36,38,45-47 However, the majority of those studies have focused on older populations that are typically at an increased risk.4 Our study is the first to demonstrate the effectiveness of an exercise intervention in young Qatari adults, when this age-group is not commonly known to be at an increased risk. Limited number of exercise interventions have focused on a university age-students, mainly focused on psychological factors such as health-related behaviours, or approach-avoidance achievement and less on the cardiovascular prevention.48,49 However, none were have focused on this age-group in the GCC region, despite stating the necessity of conducting such interventions.50-52 Therefore, results of this study could inform further research within a university workplace, particularly in the GCC region.

LIMITATIONS

The analyses of combined physical capacity and health risks factors for campus students in this study may provide a baseline for effective workplace PA interventions. We have used a validated assessment approach that relied on several direct physiological measurements of BF%, BMI and BP that have been shown to be effective to plan an university based PA intervention.7,53 However, generalizing the results of this study
across age and gender matched-groups needs to relay on a larger sample size than we were able to involve within this intervention program. The diet was not controlled which could have influenced on changes in some of the variables we have tested.

CONCLUSION

Our results suggest that overweight, obesity and physical inactivity are prevalent among young adult Qataris. Targeting those who are at risk with a physical activity programme demonstrated substantial reduction in CVD risk factors indicated by reduced blood pressure and body fat percentage. Combining health and exercise assessments with a follow up physical activity intervention can be effective strategy to reduce CVD risk factors within university campus. Interventions within the university campus-workplace reaching students and employees, alongside wider strategies to increase physical activity levels in the workplace are very much needed, and Qatar could utilize its benefits to improve society’s health significantly.

DISCLOSURE

This study was made possible by a Qatar Foundation’s Qatar National Research Fund grant award (UREP 12-048-3-009).

ACKNOWLEDGEMENT

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES


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Reward Deficiency Syndrome in Children: Obesity and Metabolic Disorders are Associated with the SNP TaqIA C32806T of the DRD2 Gene

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ABSTRACT

Background: Reward Deficiency Syndrome (RDS) is a hypo-dopaminergic state that predisposes to obsessive-compulsive behaviors. Obesity is part of RDS since the individual is predisposed to reward-driven eating behavior that leads to overeating. The allele A1 of the SNP C32806T in Dopamine D2 receptor gene (DRD2) is associated with reduction of DRD2 levels and higher BMI in adults. DRD2 are expressed in beta cells and modulate insulin secretion. The aim of this study is to investigate the relation between this SNP and obesity and metabolic alterations in children.

Methods: Fifty five obese children and 50 healthy controls were analyzed for DRD2 Taq1A polymorphism Genotyping was performed by polymerase chain reaction and restriction fragment length polymorphism. Glucose, insulin and lipid profile were measured. The Homeostatic model assessment (HOMA) was calculated.

Results: We found three genotypes: A1A1(12,4%), A1A2(33,3%) and A2A2(54,3%). The A1 allele was more present in: obese than in euthrophic (34,5%*23%), in children with altered HOMA ß (38,2% * 24,6%), children with altered Total Cholesterol (35,2%*19,5%) and lower levels of triglycerides. Children were divided in 4 subgroups in accordance to the function of pancreatic beta cells and BMI-Z; subgroups with normal secreting pancreatic beta cell demonstrated significant difference for allelic and genotypic distribution, with lower presence of A1A1 and A1A2 genotypes and higher presence of A2 allele.

Conclusions: Besides confirming the association with childhood obesity, our results show for the first time that: A1 allele is associated with TC≥170 mg/dl, lower TG levels and HOMA ß ≥175. A2 allele is associated with normal HOMA ß, being a protective factor for pancreatic secretion. The recognition of predisposed individuals through determinations of risks polymorphisms can lead to new paths for treatment and prevention of metabolic abnormalities.

KEYWORDS: Childhood obesity; DRD2 gene; HOMA; Dopamine; Genetic polymorphism.

ABBREVIATIONS: RDS: Reward Deficiency Syndrome; DRD2: Dopamine D2 receptor gene; WHO: World Health Organization; PET: Positron Emission Tomography; HOMA: Homeosta-
INTRODUCTION

Exogenous obesity is a complex disease of multifactorial etiology in which pleiotropic genetic syndromes and monogenic diseases account for only 1% of cases. It is recognized by World Health Organization (WHO) as one of the ten most important health problems in many societies. The prevalence of obesity has grown worldwide, being endemic in several developed and transition countries, and it is an important cause of morbidity and mortality in the developing world. A report published in January 2014 conducted by the Overseas Development Institute in Britain shows a general picture of the evolution of the obesity in the world in the last 30 years. Adult overweight is observed in 70% of North American’s, and in 63% of Latin American’s, a significant increase compared to 30% observed in the 80’s.

About 60% of obese children, aged 5-10 years have at least one risk factor for cardiovascular disease (hypertension, dyslipidemia, hyperinsulinemia, impaired glucose metabolism, thrombotic risk factors) and 20% of these children have two or more of these factors. In addition to metabolic complications, the obese children and adolescents also have higher incidence of asthma, sleep apnea, polycystic ovary syndrome, and psychosocial complications.

Studies show that heredity is an important factor for childhood-onset obesity. The largest study concerning the genetin of childhood obesity, where 5530 cases and 8318 controls were evaluated, showed a strong genetic influence in the development of childhood obesity.

The dopamine type-2 receptor (DRD2) gene contains 66.097 pb, it is located on chromosome 11 (q22-q23) and encodes the D2 subtype of the dopamine receptor, a transmembrane protein that couple to G-protein and inhibits adenylyl cyclase activity. This gene was included in HOGM (Human Obesity Gene Map) supported by 5 studies of candidate genes, but none of these studies had included children’s evaluation.

The DRD2 gene is highly polymorphic, and therefore, there are several SNPs described for it. The C32806T SNP, a C-T substitution located in a noncoding region of the DRD2 locus, affects the availability of the D2 receptor. The A1 allele (T) has been associated with reduced glucose metabolic rate in dopaminergic human brain regions. Variations on dopaminergic receptors and in dopamine release are involved with overeating and obesity. When exposed to high-fat diet, mice with decreased levels of DRD2 gain more weight than mice with normal levels. Studies have suggested that obese may have a decreased availability of dopamine by a striatal D2 dopaminergic receptors down-regulation mechanism. Drugs that block these receptors increase appetite and drugs that increase the central dopamine concentration have anorectic effects.

Several studies in adults suggest that increases of body mass are associated with DRD2 A1 allele and mutations in this gene have also been associated with schizophrenia and alcoholism. Positron Emission Tomography (PET) studies showed that A1 allele is associated with lower DRD2 density, and reduction of glucose metabolism in dopaminergic human brain regions.

The reward deficiency syndrome (RDS) is a hypo-dopaminergic state that predisposes to obsessive-compulsive and impulsive behaviors. Obesity is part of RDS since the individual is predisposed to reward-driven eating behavior that leads to overeating as a way to compensate the defect in dopamine levels. All components of RDS, including obesity, were related to low dopaminergic function associated with the presence of the DRD2 A1 allele. Thus, the aim of this study was to investigate the association between DRD2 gene Taq1A polymorphism and obesity, dyslipidemia and insulin resistance in children.

MATERIAL AND METHODS

Subjects

This study was conducted with 105 children and adolescents aged between 5 and 16 years (55 obese and 50 normal-weight controls) that were evaluated by a pediatric endocrinologist at Children’s Hospital Goiânia. Exclusion criteria were: overweight, malnutrition, severe chronic diseases, presence of genetic syndromes, use of medications that can alter weight (glucocorticoids, growth hormone, insulin, Gonadotropin-releasing hormone-GnRH analogues, etc.).

Parents or guardians provided informed consent prior to participation in the study. Consent was approved by the Ethics Committee on Human Research at the Pontificia Catholic University of Goiás, under the protocol number 16303313.4.0000.0037. Parents or guardians answered a questionnaire focusing on lifestyle and habits of the child and family, the presence of obesity related diseases (diabetes mellitus, hypertension, dyslipidemia, myocardial infarction, and stroke), informed the height and maximum weight of each parents, excluding maternal pregnancy period, for calculation of maximum Body Mass Index (BMI) of parents.

The diagnosis of nutritional status was based on the BMI according to WHO. Anthropometric data (weight and height) were calculated based on the WHO Anthro Plus software. Itran the BMI calculation in absolute number and in Z score according to age and sex of each child. We also evaluated metabolic measurements including lipid profile, fasting glucose and insulin. The homeostasis model assessment (HOMA) for insulin resistance
Genotyping

Genotyping was performed to identify the polymorphism Taq1A (C32806T or rs1800497) of DRD2. Biological samples were obtained by collecting 5 ml of peripheral blood in EDTA. Genomic DNA was isolated from whole blood using Illustra blood genomic Prep Mini Kit (GE Healthcare, United Kingdom) and stored in -20 °C until further processing.

To evaluate the DRD2 polymorphism we performed Restriction fragment length polymorphism polymerase chain reaction (RFLP-PCR) according to Jönsson, et al. Amplification reactions were prepared to a final volume of 50 μL of solution containing approximately 100 ng of DNA. The reactions were prepared with 2 mM of MgCl₂, 50 mM of KCl, 15 mM of Tris-HCl (pH 8.4), 10 pmol of primers, 0.2 mM of each dNTPs, and 1 U of Taq DNA polymerase (Promega Corporation, EUA). The thermocycling protocol was: initial denaturation of 95 °C for 3 min followed by 30 cycles of denaturation at 95 °C for 30 seconds, annealing at 58 °C for 30 seconds and extension at 72 °C for 60 seconds, and the extension at 72 °C for 5 min. The sequence of the primers used in the RFLP-PCR reaction were MP3 primer (5’- ACCCTTCCTGAGTGTCATCA-3’) and MP4 primer (5’- ACGGCTGGCCAAGTTGTCTA-3’) producing an amplicom of 310 pb.

The restriction enzyme was carried out using a final volume of 25 μL, containing 8 μL of the PCR product, 2.5 μL of buffer, and 1 unit of the enzyme TaqIA. The solution remained for 1 hour at 65 °C in a water bath. The restriction resulted in two fragments, one of 130 bp and another of 180 bp.

The amplicons and the restriction fragments were visualized by 1.5% agarose gel electrophoresis, submitted to an electric field of 10 V/cm, for one and a half hour. The PCR products were stained with ethidium bromide 0.5 mg/mL and documented using the Video Documentation System (VDS®, Amersham Bioscience, EUA), connected to a microcomputer with a capture system and analysis of 21 images (Imagemaster®, Amersham Bioscience, EUA).

Individuals with genotype A1/A1 (TT) do not have the site for the restriction enzyme Taq1A, therefore producing only undigested fragments of 310 pb. Individuals with genotypes A2/A2 (CC) after the action of restriction enzyme Taq1A produce two fragments, 180 pb and 130 pb. Finally, individuals with heterozygous genotype A1/A2 (CT) show three fragments, 310 pb, 180 pb and 130 pb.

Statistical Analysis

Metabolic measurements, HOMA IR, HOMA β, parents BMI, and child Z-BMI were correlated with polymorphism using SPSS17 Statistics software. Data was analyzed with the X2 test, Odds Ratio (OR) and Analysis of variance (ANOVA). All tests were considered statistically significant at p≤0.05 with 95% of confidence interval.

RESULTS

Anthropometric and clinical analysis revealed 55(52.4%) obese and 50(47.6%) eutrophic children. In the first group, 28(50.9%) were female and 27(49.1%) were male, and in the second group 27(54%) were female and 23(46%) were male. Both groups were similar to age and gender. There were significant differences (p<0.05) between the two groups for weight, height, BMI-Z, parents BMI, insulin, HOMA-IR, HOMA-β, and HDL-C (Table 1).

Genotypic distribution of DRD2 Taq1A (C32806T or rs1800497) was: 12,4% A1A1, 33,3% A1A2, and 54,3% A2A2. This distribution showed higher proportion to A1A1 and A1A2 in the obese group, and A2A2 in the eutrophic group, but this was not significantly different. Allelic distribution was significantly different (p<0.05) and there was a 1.3 RR for obesity in those who carried the A1 allele (Table 2).

Children were evaluated in groups according to the presence of allele A1, the A1A1+A1A2 group being the “risk genotype” and the A2A2 group providing the “no risk genotype”. This analysis showed statistical significance for weight, BMI-Z, mother BMI and TG (Table 3). The evaluation of genotypic distribution showed significant differences for BMI-Z, father BMI and TG (Table 4).
### Table 1: Anthropometric and clinical characteristics of obese and eutrophic groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Obese</th>
<th>Eutrophic</th>
<th>( \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>9.6 ± 1.8</td>
<td>10.2 ± 2.3</td>
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<tr>
<td>Weight (kg)</td>
<td>56.6 ± 15.6</td>
<td>30.2 ± 7.6</td>
<td>&lt;0.0001*</td>
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<tr>
<td>Height (cm)</td>
<td>142.5 ± 10.2</td>
<td>135.5 ± 12.9</td>
<td>0.013*</td>
</tr>
<tr>
<td>Z BMI</td>
<td>3.19 ± 0.9</td>
<td>-0.6 ± 0.6</td>
<td>&lt;0.0001*</td>
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<tr>
<td>Mother BMI (kg/m²)</td>
<td>29.2 ± 5.3</td>
<td>23.46 ± 2.6</td>
<td>&lt;0.0001*</td>
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<td>Father BMI (kg/m²)</td>
<td>31.88 ± 4.6</td>
<td>26.18 ± 2.9</td>
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</tr>
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<td>Fasten Glucose (mg/dl)</td>
<td>84.82 ± 5.2</td>
<td>86.02 ± 5.7</td>
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<tr>
<td>FastenInsulin (U/l/ml)</td>
<td>12.44 ± 5.8</td>
<td>6.37 ± 2.4</td>
<td>&lt;0.0001*</td>
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<td>Homa IR</td>
<td>2.64 ± 1.3</td>
<td>1.36 ± 0.5</td>
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<td>Homa ß</td>
<td>212.23 ± 96.5</td>
<td>107.34 ± 43.7</td>
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<td>TC (mg/dl)</td>
<td>167.05 ± 24.3</td>
<td>165.7 ± 19.7</td>
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<td>HDL-C (mg/dl)</td>
<td>40.44 ± 5.7</td>
<td>48.98 ± 8.4</td>
<td>&lt;0.0001*</td>
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<td>LDL-C (mg/dl)</td>
<td>109.62 ± 5.9</td>
<td>101.2 ± 18.4</td>
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<td>TG (mg/dl)</td>
<td>86.73 ± 31.0</td>
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</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median ±SD</th>
<th>Median ±SD</th>
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<tr>
<td>Years (months)</td>
<td>119.6 ± 29.85</td>
<td>118.3 ± 31.24</td>
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<td>Weight (Kg)</td>
<td>48.86 ± 21.66</td>
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<td>Height (cm)</td>
<td>141.5 ± 12.05</td>
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<td>Mother BMI (kg/m²)</td>
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<td>25.32 ± 4.18</td>
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<td>TC (mg/dl)</td>
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<td>HDL-C (mg/dl)</td>
<td>73.62 ± 29.12</td>
<td>91.91 ± 44.71</td>
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<tr>
<td>LDL-C (mg/dl)</td>
<td>44 ± 7.98</td>
<td>44.93 ± 11.13</td>
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</tr>
<tr>
<td>TG (mg/dl)</td>
<td>102.79 ± 23.65</td>
<td>107.98 ± 28.25</td>
<td>0.315</td>
</tr>
</tbody>
</table>

**Table 2: Allelic distribution of obese and eutrophic groups.**

<table>
<thead>
<tr>
<th>AllelicDistribution</th>
<th>Obese Group (%)</th>
<th>Eutrophic Group (%)</th>
<th>RR</th>
<th>( \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>38(34.5)</td>
<td>23(23)</td>
<td>1.2892</td>
<td>0.05*</td>
</tr>
<tr>
<td>A2</td>
<td>72(65.5)</td>
<td>77(77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>110(100)</td>
<td>100(100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Anthropometric and clinical characteristics in the observed risk genotype group (A1A1+A1A2) and non-risk genotype group (A2A2).**
Allelic distribution was compared with groups classified according to the references values for normality of TC (<170 mg/dl-normal range or ≥170 mg/dl-elevated level) and HOMA β (<175-normal or ≥175-altered). We observed significant difference for allelic distribution in children with TC<170 mg/dl or ≥170 mg/dl and in children with HOMA ß<175 or ≥175. The RR for A1 allele was 1.5 for HOMA ß≥175 (Tables 5 and 6). Associations between the A1 allele and TC ≥170 mg/dl and HOMA ß≥175 have not been described in the literature until now.

Children were divided in 4 subgroups in accordance to the function of pancreatic beta cells and BMI-Z: obese with normal HOMA ß (OßN), obese with altered HOMA ß (Oß↑), eutrophic with normal HOMA ß (EßN) and eutrophic with altered HOMA ß (Eß↑). Twenty six (47,3%) and 29(52,7%) obese children presented normal index and altered index, respectively. In the eutrophic group 45(90%) presented normal index and 5(10%) altered index. Allelic and genotypic distribution is shown in Tables 7, 8, 9 and 10. Subgroups with normal secreting pancreatic beta cell (OßN e EßN) demonstrated significant difference for allelic and genotypic distribution, with lower presence of A1A1 and A1A2 genotypes and higher presence of A2 allele.

| Table 4: Anthropometric and clinical characteristics observed in the genotype groups. |
|-------------------------------|-------------------|-------------------|
| Variables                      | Median            | Median            |
| Z BMI                          | 1,948             | 1,977             |
| Mother BMI (kg/m²)             | 27,66             | 27,95             |
| Father BMI (kg/m²)             | 33,29             | 28,65             |
| Glucose (mg/dl)                | 84,92             | 85,43             |
| Insulin (UI/ml)                | 11.2              | 10.08             |
| HOMA IR                       | 2.346             | 2.14              |
| HOMA ß                         | 201.96            | 174.85            |
| TC (mg/dl)                     | 153               | 164.11            |
| HDL-C (mg/dl)                  | 40.07             | 45.46             |
| LDL-C (mg/dl)                  | 97.15             | 104.89            |
| TG (mg/dl)                     | 82.84             | 70.2              |
| N (%)                          | 13(100)           | 35(100)           |

BMI: Body Mass Index; Z BMI: Z score for BMI; HOMA: Homeostasis model assessment; IR: Insulin Resistance; ß: beta cell function; TC: Total Cholesterol; HDL-C: High-density lipoprotein; LDL-C: Low-density lipoprotein; TG: Triglycerides; SD: Standard Deviation.

| Table 5: Allelic Distribution in the patients with TC<170 and TC≥170. |
|-----------------|-----------------|-----------------|
| Allele A1       | TC < 170(mg/dl) n(%) | TC ≥ 170(mg/dl) n(%) | p    |
| A1              | 16(19,5)        | 45(35,2)         | 0,0249*   |
| A2              | 66(80,5)        | 83(64,8)         |        |
| Total           | 82(100)         | 128(100)         |        |

| Table 6: Allelic Distribution in the patients with HOMA ß<175 and HOMA ß≥175. |
|-----------------|-----------------|-----------------|
| Allele A1       | HOMA ß< 175 (%) | HOMA ß ≥ 175 (%) | RR   |
| A1              | 35(24,6)        | 26(38,2)         | 1,5121 0,0367* |
| A2              | 107(75,4)       | 42(61,8)         |        |
| Total           | 142(100)        | 68(100)          |        |

RR: Relative Risk.

| Table 7: Genotypic distribution in the obese subgroups with normal secreting pancreatic beta cells (OßN) and altered secreting pancreatic beta cells (Oß↑). |
|-----------------|-----------------|-----------------|
| Genotype        | n(%)            | X²   | p    |
| A1A1            | 2(7,7)          | 7,923| 0,019* |
| A1A2            | 11(42,3)        | 11(37,9)   | 12(41,4) |
| A2A2            | 13(50)          | 26(100)    | 29(100)   |
| Total           | 55(100)         |        |

| Table 8: Genotypic distribution in the eutrophic subgroups with normal secreting pancreatic beta cells (EßN) and altered secreting pancreatic beta cells (Eß↑). |
|-----------------|-----------------|-----------------|
| Genotype        | n(%)            | X² | p    |
| A1A1            | 4(8,9)          | 21,733| <0,0001* |
| A1A2            | 12(26,7)        | 1(20)   | 3(60)   |
| A2A2            | 29(64,4)        | 45(100)  | 5(100)   |
| Total           | 50(100)         |        |

| Table 9: Allelic distribution in the obese subgroups with normal secreting pancreatic beta cells (OßN) and altered secreting pancreatic beta cells (Oß↑). |
|-----------------|-----------------|-----------------|
| Allele A1       | n(%)            | X²   | p    |
| A1              | 15(28,8)        | 8.481| 0,0036*   |
| A2              | 37(71,2)        | 35(60,3)    | 2,09 0,1486 |
| Total           | 52(100)         | 58(100)     |
We compared allelic distribution between these 4 subgroups, and the groups O\(\beta\)↑ and E\(\bar{\beta}\)N were statistically different. Obese children with altered HOMA B have a major presence of A1 allele (Table 11).

<table>
<thead>
<tr>
<th>O(\beta)↑</th>
<th>E(\bar{\beta})N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele</td>
<td>(n(%))</td>
</tr>
<tr>
<td>A1</td>
<td>23(39.7)</td>
</tr>
<tr>
<td>A2</td>
<td>35(60.3)</td>
</tr>
<tr>
<td>Total</td>
<td>58(100)</td>
</tr>
</tbody>
</table>

Table 10: Allelic distribution in the eutrophic subgroups with normal secreting pancreatic beta cells (E\(\bar{\beta}\)N) and altered secreting pancreatic beta cells (E\(\beta\)↑).

DISCUSSION

Anthropometric and clinical analysis revealed some differences between the obese and eutrophic groups. The significant difference in weight and BMI-Z is expected and is itself the definition of each group. The greater height observed in the obese group is in accordance with usual clinical findings in this group of children, and is confirmed by clinical studies showing that obese children are taller than their peers of same age. However, since they have accelerated bone maturation, their growth occurs for a shorter period of time, not leading to changes in final adult height.25

The presence of higher levels of parents BMI of obese children corroborates studies that indicate a strong genetic component in human obesity.26-28 The children in the present study coexist in the same environment as their biological family (except for two), and therefore are exposed to the same lifestyle. It’s known that a child who has both obese parents has 80% chance of being obese, 50% if one parent is obese, and 9% when both parents are not obese.29 In our study, the mean BMI of parents is above normal in both groups. The eutrophic children group had overweight parents, consistent with the increase of overweight and obesity in the adult Brazilian population, reaching 48% of women and 50% of men.30

In this study, obese and eutrophic groups presented the same level of blood glucose, however, obese group showed higher levels of insulin, HOMA IR and HOMA B. These changes in insulin sensitivity and pancreatic beta cell secretion are related to obesity, which is an important risk factor for the development of Type 2 Diabetes Mellitus (DM2).3 The finding of lower level of HDL-C in the obese group is expected, since the presence of risk factors for cardiovascular disease in obese children is common.3,5

The TaqIA polymorphism (C32806T) of DRD2 gene is associated with decreased brain dopaminergic activity,32 and the A1 allele was related with increased BMI in adults.20,33 Few studies have been conducted to verify the association of the DRD2 polymorphism TaqIA in children and adolescents.33

In this study, we identified 34.5% and 23% for A1 allele in obese and eutrophic groups respectively, and a statistically significant association between the presence of A1 allele with childhood obesity conferring relative risk of 1.3. Studies noted a wide variation in allele frequencies, even within the same country populations. In two studies conducted with Turkish children, one of them showed 51% of the A1 allele in obese,34 while another reported only 20%.35 A Dutch study showed the frequency of 18.3% of A1 allele36 and in North American studies the frequency of the A1 allele in obese children ranged from 17%37 to 38.5%.38

The DRD2 TaqIA polymorphism was previously evaluated in children and/or adolescents among few other groups. The A1 allele was associated with obesity in one study,37 other 2 studies did not find this association;23,34 it was also described compulsive feeding behavior39 and difficulties in acceptance for healthier life style modification.36

Although TG levels were lower in the A1 allele group, this difference was not clinically relevant, since all groups showed TG in the normal range. TG levels were 20% lower in the “risk genotype” group as compared with “no risk genotype” group and was 10% lower in subjects with A1A1 genotype compared with A2A2 genotype group. Miyashita and colleagues performed a meta-analysis evaluating the effect of physical exercise on TG levels and found significant decreases in TG after short time and intermittent physical exercise. The decrease in TG levels ranged from 10% to 5 minutes practice of exercise six times per day, up to 27% for practice of 10 minutes 3 times per day.39 It was hypothesized that children with the presence of the A1 allele have the lowest TG, due to higher levels of physical activity. The presence of A1 allele contributes to the Reward Deficiency Syndrome (RDS), in which Attention Deficit/Hyperactivity Disorder (ADHD) is part,20 moreover studies assessing the Taq IA polymorphism of DRD2 gene and personality traits using the Tridimensional Personality Questionnaire demonstrate that A1 allele is associated with certain behavioral traits, with higher levels of impulsivity, extravagance, disorganization,38-42 persistence38,41 and gregarious attitude.38-42 These behavioral characteristics may lead to greater practice of physical exercise by the children with the A1 allele, and thus may explain lower TG levels.

The association of A1 allele with higher frequency of CT≥170 mg/dl is explained by the feeding behavior assigned to A1 allele carriers as a way to compensate for the RDS.

Our study demonstrated the association of impaired
function of pancreatic beta cells with A1 allele conferring a relative risk of 1.5 for HOMA $\beta \geq 175$. Clinical studies in diabetic patients and in animal studies show improvement of glucose control with the use of bromocriptine, a dopamine agonist which acts through DRD2 receptors. In 2005, Ruby and colleagues first demonstrated that DRD2 receptors are expressed in pancreatic beta cells and modulate the secretion of insulin. Study conducted in rats “knockout” for the DRD2 gene revealed that DRD2 receptors play a crucial role in insulin secretion and glucose homeostasis; mice with absence of the DRD2 receptor had a flat insulin response to glucose load, higher fasting glucose, impaired glucose tolerance and decreased beta cell mass. These results indicate that DRD2 is important for beta cell proliferation and insulin secretion, and may be considered as a growth factor essential for the control of glucose homeostasis.

For the first time, the A1 allele of the DRD2 gene is associated with alteration of glucose homeostasis in humans. The presence of this allele reduces the number of brain receptors; it is assumed that must also reduce the number of receptors on beta cells, explaining our clinical findings. The presence of the A2 allele was associated with normal HOMA $\beta$ in eutrophic and obese patients, demonstrating a protective effect of this allele in the pancreatic secretion.

CONCLUSIONS

Regarding the TaqIA (C32806T) polymorphism of DRD2 gene we observed several statistically significant results. A1 allele (T) is associated with: higher weight and children Z-BMI, conferring a relative risk of 1.3 for the presence of childhood obesity. This allele is also associated with higher BMI of the mother and father. Regarding the lipid profile, the A1 allele is associated with lower levels of TG and higher frequency of CT$\geq 170$ mg/dl.

With respect to carbohydrate metabolism, our study found an unprecedented result in the literature: the A1 allele was associated with HOMA $\beta \geq 175$, giving a relative risk of 1.5. The A2 allele was associated with normal HOMA $\beta$ in eutrophic and obese individuals, demonstrating the involvement of this allele as a protective factor for pancreatic secretion.

The major limitation of this study is the relatively small population. Even though, our research opens a new line of investigation: the relationship between early-onset obesity, the TaqIA polymorphism of the DRD2 gene and abnormality of secretion of pancreatic beta cells.

Despite widely recognized that genetic factors are important for weight gain, the actual quantitative contribution of genetics in related phenotypes is still a complex issue that needs to be clarified. The knowledge of the genetic architecture of obesity will increase our understanding of the regulation of energy balance in humans, and therefore, provide new paths for the treatment and prevention of this serious health problem. The recognition of predisposed individuals by determining risk polymorphisms can establish new pathways for the treatment and prevention of childhood obesity. We believe that in the future children will be treated based on their genomes.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ACKNOWLEDGMENTS

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33. Böettcher Y, Korner A, Kovacs P, Kiess P. Obesity genes:


Daily Calcium Intervention for a Weight-Loss Program Resulted in More Significant Decreases in Body Weight, BMI, Body Fat Mass, and Body Fat Percentage

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ABSTRACT

The purpose of this study was to assess of calcium intervention on the effectiveness of a weight-loss program for obese people. All subjects had an initial BMI (body mass index) >24 kg/m² and low calcium diet (<500 mg/d). Forty-two healthy overweight or obese people were randomly and equally divided into two groups: a Hi-Ca group (female: 16, male: 5) and a control group (female: 16, male: 5). In the Hi-Ca group, we provided two bottles of Hi-Ca drinks per day and a low energy diet (energy: 1200 kcal, carbohydrate: 55%, fat: 25%, protein: 20%) for eight weeks. In the control group, we only provided the low energy diet for eight weeks. We measured three-day food records, anthropometric and blood biochemical data at Weeks 0 and 8. Calcium intake was 964.5±75.5 mg in the Hi-Ca group and was 353.7±96.6 mg in the control group (p<0.05). After eight weeks, results showed the loss of body weight (-6.9±3.3 kg, p<0.05), BMI (-2.7±1.1 kg/m², p<0.01), body fat mass (-5.7±2.7 kg, p<0.05), body fat percentage (-4.4±1.9 %, p<0.002) and TC/HDL-C (-0.4±0.6, p<0.05) in the Hi-Ca group were significantly different from those of the control group at eight weeks. In the lipid profile, serum cholesterol, triglycerides and LDL-C concentration were significantly decreased compared with Week 0. The serum PTH (parathyroid hormone) levels in the Hi-Ca group were significantly lower compared with baseline (-5.3±10.4 pg/mL, p<0.05), which showed that the concentration of PTH and calcium intake are negatively correlated, and indicate that a high-calcium low-energy diet resulted in more significant decreases in body weight, BMI, body fat mass, and body fat percentage. Therefore, a high calcium diet increases the effectiveness of an energy-restricted diet for weight loss in overweight people.

KEYWORDS: Obesity; Energy restricted diet; Weight loss; Calcium; Parathyroid hormone (PTH).

ABBREVIATIONS: PTH: Parathyroid hormone; CVD: Cardiovascular disease; BMI: Body Mass Index.

INTRODUCTION

Obesity is recognized as one of the most significant public health problems in the world.1-3 It is a risk factor for chronic disease, such as heart disease, cancer, stroke and diabetes.4-7 Conversely, weight loss is associated with reduction of risk for Cardiovascular disease (CVD) and diabetes mellitus.4,5 To study this relationship, we assessed the impact of a dietary calcium intervention on the effectiveness of a weight loss program for obese people.

Recent findings indicate that calcium metabolism and perhaps other components of dairy products may contribute to shifting the energy balance, and thus play a role in weight reg-
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Obes Res Open J
ISSN 2377-8385

It has recently been shown that overweight people with low calcium and dairy consumption were at much greater risk of developing metabolic syndrome over a ten-year follow-up period than were overweight people who had high calcium and dairy consumption. This finding suggests that adequate calcium intake could exert a significant effect on the predisposition to a healthier metabolic profile, similar to that of a macro-nutrient-balanced diet and regular physical activity.

Increased dietary calcium without energy restriction is associated with decreased fat mass in both animals and humans and thus may play a role in the attenuation of obesity and its related health complications. The inverse association between calcium and body mass was established twenty years ago by McCarron. One possible factor to explain the relationship between calcium intake and BMI is the fatty acid binding capacity of calcium. An alternative hypothesis for explaining the anti-obesity effect of calcium links dietary calcium intake, serum 1,25-dihydroxy vitamin D concentration and adipocyte intracellular calcium concentration. A low calcium diet leads to an increase in 1,25-(OH)2-D which in turn stimulates calcium influx into adipocytes, resulting in stimulation of lipogenesis, inhibition of lipolysis and expansion of adipocyte triglyceride stores. Suppressing 1,25-(OH)2-D levels by increasing dietary inhibition of lipolysis and expansion of adipocyte triglyceride stores. Suppressing 1,25-(OH)2-D levels by increasing dietary calcium may consequently be predicted to inhibit adiposity and promote weight loss. Calcium in the form of dairy products may be more effective than elemental calcium, and high concentrations of branched chain amino acids in dairy products are responsible for this effect. The objective of the current study was to investigate the relationship between calcium intake and body composition, body fat distribution and serum lipid profile in overweight or obese subjects.

MATERIALS AND METHODS

Subjects

This study was proposed and conducted at Taipei Medical University. We recruited a total of 42 volunteer participants prior to the experiment start date. There were no significant differences between those who completed the study and those who did not on any parameters. Baseline participant characteristics are described in Table 1. Subjects were recruited via a flyer advertisement in Taipei Medical University. The subjects had to meet the following criteria: age 18-64 years; Body Mass Index (BMI) higher than 24; calcium consumption <500 mg/day (according to three-day food records); no history of chronic disease, including history of cardiovascular disease, kidney disease, liver disease, endocrine disorders, and diabetes mellitus; women were included only if they were not pregnant or breast-feeding; and no participation in another clinical trial (within six months) was permitted. Sample-size calculations were based on results from a randomized, parallel-design study, we estimated that a sample size of 20 subjects/group in the current would yield 80% power (2-tailed α=0.05) to detect a similar group difference. At the beginning of study, 70 volunteer subjects were assessed for eligibility, 28 were excluded (26 not meeting inclusion criteria, 2 declined to participate). The Research Ethics Committee, Taipei Medical University, Taiwan, approved the study and all subjects gave written informed consent before their participation.

Table 1: Physical characteristics and nutrient intake of study subjects.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hi Ca group (n=21)</th>
<th>Control group (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.0±12.0</td>
<td>35.2±11.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.7±7.7</td>
<td>164.0±6.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.2±16.2</td>
<td>80.2±10.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.0±4.4</td>
<td>29.7±2.0</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.4±12.0</td>
<td>99.0±8.1</td>
</tr>
<tr>
<td>Energy intake (kcal/d)</td>
<td>1997.0±35.6</td>
<td>2001.8±73.2</td>
</tr>
<tr>
<td>Calcium intake (mg/d)</td>
<td>320.2±93.7</td>
<td>328.2±87.7</td>
</tr>
</tbody>
</table>

1 Each value represents the mean ± SD. There were no significant differences between groups based on independent-samples t-test.

Dietary Supplementation

All subjects were randomly divided into two single-blind groups: subjects in Hi-Ca group were provided Hi calcium drinks (calcium 300 mg/pack) every breakfast and dinner for eight weeks and prescribed a low-calorie diet providing 5.2 MJ/d (1200 kcal/d) during the intervention.

Experimental Design

For the control group, we provided only a low energy diet for eight weeks. The diets for the two groups were designed to provide comparable levels of macronutrients as follows: 55% carbohydrate, 20% protein, and 25% fat. Lectures about nutrition and weight management were provided to both groups on every visit. Anthropometric measurements were taken including height, weight, and the percentage of body fat during each weekly visit. Biochemical parameters were analyzed at beginning and end of the intervention. Dietary records and counseling were used to estimate dietary intake. We educated the participants about guidelines for 1200 kcal diets and gave instruction on protein sources and food portion sizes.

Analyses of Anthropometry and Serum Lipid Profiles

Anthropometry: Height, bodyweight, and waist circumference were measured, and the BMI was then calculated (screening, 0, 8 weeks). Body composition was measured using the InBody 3.0 Body Composition Analyzer. Systolic and diastolic blood pressures were measured in the right or the left arm supported at heart level of seated participants.
Biochemical analysis: At screening, 0, and 8 weeks, blood samples were obtained following a twelve-hour fast and serum was stored at -80 °C until analysis. PTH level was determined using a commercial immunoradiometric assay. Cholesterol and triglyceride concentrations were determined enzymatically in plasma and lipoprotein fractions with an automatic immunoanalyzer. Plasma lipoprotein fractions (LDL and HDL) were isolated by ultracentrifugation.

**Determination of Serum and Urinary Mineral Status**

To monitor minerals in serum, the following laboratory parameters were determined at 0, 4, and 8 weeks: urinary calcium and serum calcium status. Serum calcium and urinary calcium were measured by the O-cresolphthalein complex colormetric method using a Hitachi 7170S auto analyzer.

**Assessment by Nutritional Survey**

Nutrition was assessed from a 3-day diet record for two weekdays and one weekend day in weeks 0, 8, and information was collected on the day the subject returned. We mainly assessed the dietary intake of total energy, macronutrients, and calcium intake during the study period based on food records are shown in Table 2. These indicate no differences in energy, macronutrient, and fiber intake, and were very close to the recommended amounts of 55%, 20%, and 25%, respectively. After eight weeks, results showed that the calcium intake was 964.5±75.5 mg in the Hi-Ca group and was 353.7±96.6 mg in the control group (p<0.05).

As shown in Table 3, body weight, body mass index, body fat mass, body fat mass percentage, waist circumference and waist-hip ratio of the two groups decreased significantly after eight weeks of weight loss intervention (p<0.05 for all). Moreover, the loss of body weight (-6.9±3.3 kg, p<0.05), BMI (-2.7±1.1 kg/m², p<0.01), body fat mass (-5.7±2.7 kg, p<0.05), body fat percentage (-4.4±1.9 %, p<0.002) in the Hi-Ca group differed significantly from those of control group after eight weeks.

**Blood Glucose and Serum Lipids**

As for lipid profiles, serum cholesterol, triglyceride and LDL-C concentration at Week 8 were significantly lower compared with Week 0. TC/HDL-C ratio was significantly lower in
the Hi-Ca group than in the control group (p<0.05). There was no statistically significant difference in blood glucose levels and blood pressure between the two groups (Table 4).

**Calcium Intake and Body Composition**

The Hi-Ca group was significantly lower in serum PTH (parathyroid hormone) compared with baseline (-5.3±10.4 pg/mL, p<0.05) at Week 0, which showed that the concentration of PTH and calcium intake were negatively correlated, indicating that using a high calcium low energy diet for weight loss produced more significant decrease in body weight, BMI, body fat mass, and body fat percentage. Significant negative correlations were observed between calcium intake changes and PTH levels, as shown in Table 5. (p<0.001). Significant negative correlations were also observed between calcium intake changes and body weight change (p<0.0001), body mass index (p<0.0001), body fat mass (p<0.0001), body fat mass percentage (p<0.0001), and waist circumference (p<0.027).

**DISCUSSION**

This study demonstrates that an energy restricted diet (1200 kcal/day) for eight weeks can lead to a significant reduction in weight, BMI, body fat mass and body fat percentage. Modest weight loss in obese individuals (5-10% of initial body weight) is likely to improve their health in the short term by reducing the severity of comorbidities associated with obesity.15,24

Our findings also indicate that a high calcium diet can lead to greater reduction in weight, BMI, body fat mass, and body fat mass percentage. Zemel, et al. showed the effect of an
energy-restricted diet on weight and fat loss (providing either 400-500 mg/day from dairy products, or 1200-1300 mg/day from an additional 800 mg of calcium carbonate, or from an additional three servings of dairy products) in 32 obese or overweight women. Their results indicated that increasing dietary calcium significantly augmented weight and fat loss secondary to caloric restriction.9

To date, numerous observational studies have identified a strong inverse relationship between weight and dietary calcium and dairy product intake.25 A low calcium diet leads to an increase in 1,25(OH)2-D3, which in turn stimulates calcium influx into adipocytes, resulting in stimulation of adipocyte triacylglyceride stores. Suppressing 1,25(OH)2-D3 levels by increasing dietary calcium could thus be predicted to inhibit adiposity and promote weight loss. High dietary calcium intake is associated with reduced 1,25(OH)2-D3 levels which in turn act to decrease calcium influx into the cell. These modifications eventually stimulate lipolysis and inhibit lipogenesis in the adipocytes.27-29 Another mechanism that might explain the relationship of calcium consumption and adiposity is the effect of calcium on triglyceride absorption from the intestinal tract. Large amounts of calcium in the gastrointestinal tract may reduce absorption by precipitating insoluble fatty acid calcium soaps.18,30-33

Hi-Ca group (n=21)

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 8</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG (mg/dL)</td>
<td>115.1±48.1</td>
<td>84.8±24.0*</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>183.1±24.5</td>
<td>157.2±25.3*</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>115.2±21.9</td>
<td>97.4±20.7*</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>40.9±12.9</td>
<td>37.6±9.9 a</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>4.8±1.2</td>
<td>4.4±1.0 a</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>102.3±20.1</td>
<td>96.7±11.4 a</td>
</tr>
</tbody>
</table>

Control group (n=21)

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 8</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG (mg/dL)</td>
<td>127.7±60.1</td>
<td>109.2±58.3*</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>200.6±31.6</td>
<td>178.0±32.7*</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>121.1±27.6</td>
<td>109.5±30.0*</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>53.4±10.1</td>
<td>46.6±8.2 a</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>3.9±1.9</td>
<td>3.9±1.0</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>94.9±9.9</td>
<td>91.0±8.9</td>
</tr>
</tbody>
</table>

1 Each value represents the mean±SD.
2 TC: total cholesterol, TG: triglyceride, LDL-C: low density lipoprotein-cholesterol, HDL-C: high density lipoprotein-cholesterol.
3 Glucose: fasting plasma glucose (normal range for Glucose=80-105 mg/dL)
4 The Week 8 values are significantly different from Week 0, p<0.05.
5 Values are significantly different with control group, p<0.05.
6 Values are significantly different with Hi-Ca group, p<0.05.

Table 4: Serum lipid and glucose profiles before and after the weight-loss intervention and change in variables between measurement periods.

We did not observe a significant difference between groups in terms of a decrease in fasting plasma glucose and blood pressure in response to the intervention. Indeed, the Coronary Artery Risk Development in Young Adults Study showed that abnormal glucose homeostasis incidence decreased with increasing dairy intake in overweight persons.13 Therefore, better understanding is still needed to determine whether the benefit of the calcium-induced improvement in glucose levels and blood pressure can be attributed to dairy products.

Consumption of a dairy calcium rich diet confers protection against loss of lean body mass during energy restriction (Hi-Ca group: -0.7±1.1 kg; Control group: -1.2±1.3 kg). This outcome may be attributable to the high proportion of BCAA (branched chain amino acid, including leucine, isoleucine and valine), found in dairy proteins. They play a specific metabolic role as energy substrates and in the regulation of muscle protein synthesis.9,38-40

Low calcium intake increases PTH, resulting in increased cellular calcium. Supporting the role of PTH in obesity, a positive correlation between serum intact PTH and both BMI and fat mass has been observed.10,41-43 In this study, negative correlations with PTH levels did reflect the differences in the Hi-Ca group (Hi-Ca group: -5.3±10.4 pg/mL; Control group: +11.5±14.3 pg/mL). Significant negative correlations were observed between PTH level and calcium intake changes. Significant negative correlations were likewise observed between calcium intake changes and body weight change, body mass index, body fat mass, body fat percentage, and waist circumference. For instance, in a study on 302 healthy volunteers, Parikh et al. found significantly lower plasma 1,25(OH)2-D3 levels in obese than in non-obese subjects.44 In addition, PTH has also been
shown to regulate adipocyte intracellular calcium, and it has been proposed as a potential mediator of the anti-obesity effect of dietary calcium. In support of the role of PTH in obesity, positive correlations between serum PTH and BMI and fat mass have been reported by several studies.

In conclusion, we suggest that a high calcium diet increases the effectiveness of calorie-restriction for weight loss in overweight and obese people, while also improving cardiovascular disease risk profile. Further research could examine possible mechanisms on calcium and adipose tissue accumulation.

STRENGTHS AND LIMITATIONS

The strengths of this study include the objectively investigated the relationship between calcium intake and body composition, body fat distribution and serum lipid profile in overweight or obese subjects. We found a high calcium diet increases the effectiveness of an energy-restricted diet for weight loss in overweight people resulted in more significant decreases in body weight, BMI, body fat mass, and body fat percentage. However, physical activity were based on self-reported data, baseline physical characteristics were similar in the Hi-Ca group and control group. All subjects were asked to keep regular physical activity and life style. We did not track physical activity during intervention. Future research could examine their physical activity levels during study.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Post-Meal Exercise may Attenuate the Glycemic Response to a Carbohydrate Load: Important Implications for Adults who are Obese, with Pre-Diabetes or Diabetes, and/or At-Risk for Dementia

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ABSTRACT

Obese individuals are at risk for insulin resistance and type 2 diabetes. Both obesity and diabetes are known risk factors for dementia, already a recognized global public health issue. Up to one-third of Alzheimer-type dementia may be attributed to potentially-modifiable risk factors such as the prevention of obesity and diabetes; physical exercise, particularly post-meal exercise, can play an important role in such prevention. This paper reviews research on the link between obesity and insulin resistance related to the conditions of pre-diabetes and diabetes, the consequences of elevated blood glucose (hyperglycemia) that result from a carbohydrate-rich diet and insulin resistance, the potential short and long term health consequences of elevated blood glucose, and the promising effects of post-meal exercise to stabilize blood glucose levels after consuming a carbohydrate load. Mitigating elevated blood glucose after consumption of snacks and meals in obese adults who are at-risk for, or who have diabetes, could improve glycemic control, decrease the need for medication (or decrease the dosages needed), delay the onset of long term complications of the diabetes, and decrease dementia risk. Further, facilitating stable levels of blood glucose in adults diagnosed with dementia through regular post-meal light exercise may positively affect mood and behavior, important aspects of dementia management, as well as physical health. If post-meal exercise does prove to effectively blunt the blood glucose spike after a meal, it could be a low-cost convenient method to prevent the damaging consequences of elevated blood glucose.

KEYWORDS: Diabetes; Dementia; Elevated blood glucose; Insulin resistance; Obesity; Post-meal exercise; Prevention.


INTRODUCTION

Obesity, especially abdominal obesity, increases the risk for pre-diabetes and Type 2 Diabetes Mellitus (T2DM). Through changes in the microvascular and macrovascular systems, as well as inflammatory mechanisms, diabetes is a known risk factor for dementia, a progressive, neurological and life-limiting disease. Midlife obesity is a further risk factor...
for developing dementia. Thus, the rising tide of obesity, with its association with pre-diabetes and T2DM, has the potential to profoundly worsen the prevalence of dementia, already a recognized global public health issue.

In 2012, 28 million Americans had T2DM, 86 million had pre-diabetes, and the prevalence of these conditions is increasing. Pre-diabetes and diabetes are characterized by insulin resistance, in which case insulin is not optimally effective in inhibiting liver glycogenolysis (referred to as liver insulin resistance) or stimulating the transport of glucose from the circulation into skeletal muscle cells and adipocytes. The end result of insulin resistance is elevated Blood Glucose (BG); hyperglycemia. Fasting BG, the Oral Glucose Tolerance Test (OGTT), and glycated hemoglobin (HbA1c) are used to diagnose pre-diabetes and diabetes. Fasting BG (measuring plasma glucose after not eating for at least 8 hours) is often the initial test done. The more substantial OGTT follows fasting BG and involves consumption of a beverage containing 75 gm of glucose with BG measured every 30 min for at least 2 hrs. The HbA1c test indicates a person’s average blood glucose levels over the preceding 2-3 months. Blood test criteria to diagnose pre-diabetes and diabetes are shown in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>HbA1c [A1C] (percent)</th>
<th>Fasting Plasma Glucose (mg/dL)</th>
<th>Oral Glucose Tolerance Test (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>6.5 or above</td>
<td>126 or above</td>
<td>200 or above</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>5.7 to 6.4</td>
<td>100 to 125</td>
<td>140 to 199</td>
</tr>
<tr>
<td>Normal</td>
<td>About 5</td>
<td>99 or below</td>
<td>139 or below</td>
</tr>
</tbody>
</table>

Definitions: mg: milligram; dL: deciliter
For all three tests, within the pre-diabetes range, the higher the test result, the greater the risk of diabetes.
Source: Adapted from American Diabetes Association. Standards of medical care in diabe-
Table 1: Blood test levels for the diagnosis of diabetes and pre-diabetes.

Short-term consequences of hyperglycemia include fatigue, blurred vision, poor wound healing, increased thirst and urination, numbness or tingling in the extremities, and increased infections. Long-term complications of T2DM can be devastating, and include cardiovascular disease, retinopathy, neuropathy, and nephropathy, as well as cognitive decline.

THE LINK BETWEEN OBESITY, INSULIN RESISTANCE, AND DEMENTIA

Obese individuals are at increased risk for insulin resistance for a number of reasons, and the mechanisms are described in an excellent review article by Qatanani and Lazar. Greater fat mass results in elevated levels of Free Fatty Acids (FFA), which affect the circulating levels of the secreted hormones collectively called “adipokines.” Laboratory studies have shown that the adipokine resistin and Retinol-binding protein 4 (RBP4) are elevated with obesity, although the role in humans is uncertain at this point. In a recent review, Kilian and her colleagues identified investigations that describe the role of adipokines in the link between obesity and dementia. These investigations suggest that obesity, through impaired cerebral blood flow, is associated with brain atrophy and deep (subcortical) hemispheric white matter changes that affect neurons, glia, vascular cells, the permeability of the blood-brain-barrier and the production of axonal myelin by oligodendrocyte cells in the brain. The investigations raise the possibility that adipokines contain important clues to transient or permanent cognitive decline as a result of impaired neurovascular structure and function. Small vessel (white matter) infarcts are strongly associated with diabetes, insulin resistance, and hyperlipidemia. These micro-infarcts, along with micro-bleeds, increase dementia risk and are associated with reduced glucose uptake in the frontal lobe and cortical atrophy. Weight control and maintaining blood glucose at an optimal level are among the recommended strategies to control vascular risk factors, promote vascular health and lessen the risk for dementia.

Adipocytes (cells that comprise fat tissue) also produce the hormone cortisol when cortisone, the inactive form, is converted to cortisol by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1). Adipocyte 11βHSD1 levels are increased in obese humans and contribute to obesity-related insulin resistance, resulting in increased influx of cortisol to the liver via the portal vein. This may partly explain why visceral fat is associated with increased insulin resistance. Of equal importance, increased levels of cortisol in cerebrospinal fluid have been associated with faster cognitive decline in adults with Mild Cognitive Impairment and Alzheimer-type dementia, reflecting hyperactivity of the hypothalamic-pituitary-adrenal axis. This hyperactivity may precede clinical symptoms of dementia, and may be a particular issue for adults who carry the APOE e4 allele, a genetic risk factor for dementia.

Adipose tissue is now recognized as an important and active part of the immune system. Consistent, strong evidence indicates that obesity-related chronic inflammation is linked to insulin resistance, T2DM, and dementia. Inflammatory markers (cytokines; often linked with adipokines and termed adipocytokines) including Interleukin-6 (IL-6), Tumor necrosis factor alpha (TNFα), and C-reactive protein (CRP) are elevated in obese, insulin resistant individuals, and increased levels of these inflammatory markers are predictive of the development of T2DM and other pathological conditions. Macrophages, which generate and secrete inflammatory cytokines, accumulate in adipose tissue. Interestingly, inhibition of macrophage infiltration in adipocytes of obese rodents reduces insulin resistance.

Alterations in neurobiology in the obese may also contribute to insulin resistance. Circulating leptin (produced by adipocytes) and insulin (produced by the pancreas) levels are proportional to fat mass, and provide input to the regions of the hypothalamus involved in appetite regulation and substrate metabolism. Both insulin and leptin receptors in the brain are necessary for normal insulin action. Central administration of leptin in insulin resistant rodents attenuates insulin resistance, and inhibition of hypothalamic insulin receptors results in liver
insulin resistance. 33

Other possible explanations for the role of obesity in the development of insulin resistance include ectopic lipid storage in the liver and muscle, oxidative stress, and Endoplasmic Reticulum (ER) stress that suppresses insulin signaling. 15 Obesity also is associated with mitochondrial dysfunction that results in excessive intracellular lipid accumulation, excessive fat storage in liver and muscle tissue, increased fatty acid metabolites and Reactive Oxygen Species (ROS) that interfere with insulin signaling.

POTENTIAL HEALTH CONSEQUENCES OF ELEVATED BLOOD GLUCOSE: MECHANISMS

The health consequences associated with elevated Blood Glucose (BG) levels are well documented in the literature. Elevated BG levels increase the glycosylation of body proteins and lead to increased Advanced glycosylated end products (AGEs). 34-36 AGEs are associated with accelerated aging and the progression of numerous health conditions such as Alzheimer’s disease, diabetes, cardiovascular disease, and stroke. 5-7,37-39 The consumption of sugar and refined carbohydrates results in BG elevation that is proportional to the accumulation of AGEs. 40

Elevated blood glucose also can contribute to chronic inflammation. 41,42 Chronic inflammation is mediated by the immune system; cells of the immune system enter tissues and release chemicals that perpetuate the inflammatory state, resulting in damage to healthy tissues. A recent systematic review describes studies in which high glycemic load diets have been associated with higher concentrations of circulating inflammatory markers. 43 High blood glucose causes inflammation through several mechanisms that increase the production of free radicals and other pro-inflammatory chemicals. Chronic inflammation is associated with a number of chronic diseases, including cardiovascular disease, diabetes, cancer and Alzheimer’s disease. 44-47

Thus, prevention of T2DM is of utmost importance. For obese individuals, one of the recommendations to prevent pre-diabetes or progression to T2DM is to exercise at a moderate pace for at least 150 min per week. 48,49 It is well known that physical activity improves insulin sensitivity in both healthy and insulin resistant individuals. 50 However, compliance with current exercise recommendations is poor, with self-reported compliance rates of about 35% for those with T2DM. 51 Emerging evidence 52-59 suggests that a short bout of post-meal exercise in particular can attenuate the spike in BG after consumption of carbohydrates, which may be advantageous for those with and without diabetes, including those with dementia. Knowing that a short bout of exercise after consumption of a carbohydrate load could specifically decrease the spike in BG after carbohydrate consumption may be more motivating for compliance than exercising for general improvements in glycemic control.

Ideally, consumption of refined and simple carbohydrates would be avoided to prevent blood glucose spikes. However, it is difficult for many to restrict or eliminate such foods from the diet, especially in light of increasing evidence for sugar addiction. 60 Only about 50% of those with chronic illnesses adhere to recommended lifestyle changes. 51 Adherence rates to dietary recommendations in those with T2DM appear to be especially poor; a large multi-national study including North America, indicated a self-reported dietary adherence rate of 37% among those with T2DM. 51 Tan and colleagues found that only 16.4% of surveyed individuals with type 2 diabetes indicated they adhered to dietary regimens recommended by dietitians. 62 Vijan and colleagues found that people with type 2 diabetes rated strict diet as a major burden. 63 Moreover, adults with dementia tend to favor foods with simple carbohydrates, Saturated Fatty Acids (SFA) and simple sugars. Hsu and Kanoski 64 suggest that consumption of these foods can adversely affect the neuronal structure, plasticity, and function of the hippocampus, an area of the brain critically important for memory and learning. These investigators speculate that adverse effects result from elevated secretion of beta-amyloid in the small intestines, its increased circulation within the vascular system, and subsequent damage to the blood-brain-barrier. This in turn increases the vulnerability of the hippocampus to beta-amyloid build-up and other circulating toxins.

DIETARY CARBOHYDRATE AND BLOOD GLUCOSE LEVELS: CONSEQUENCES OF POST-MEAL HYPERGLYCEMIA

After consumption of a carbohydrate source, blood glucose levels rise, reaching a peak about 1 hr after ingestion, but this peak could be 30-min to 2 hrs, depending on the composition, quantity, and timing of the meal or snack. 65 The pancreas releases insulin in response to an elevation in BG, which facilitates glucose entry into cells and glucose storage as glycogen in the liver, lowering BG to maintain glucose homeostasis. Some foods result in a slower rise and a lower peak of blood glucose than others. Glycemic Index (GI) reflects the degree to which different foods ingested in amounts that provide 50 gm carbohydrate increase blood glucose. Some prefer to consider foods in terms of Glycemic Load (GL) which is calculated as GI×grams of carbohydrate consumed/100. 66 Foods that are high in simple and refined carbohydrates have the highest GIs. Consumption of high GI foods results in higher and more rapid increases of blood glucose than lower glycemic index, which could influence inflammation and AGEs. Studies have shown that low glycemic index diets decrease inflammation and formation of AGEs. 40,41,67

In a healthy individual, BG elevates no higher than 140 mg/dL after a carbohydrate load. 68,69 A value above that would be considered post-meal hyperglycemia. Post-meal hyperglycemia is very common in those with T2DM, but can occur before clinical diagnosis. 70 The International Diabetes Federation (IDF) has concluded that post-meal hyperglycemia is harmful, associated with increased risk for macrovascular disease, retinopathy,
cancer, impaired cognitive function in the elderly with T2DM, increased carotid intima-media thickness, decreased myocardial blood volume and blood flow, and increased oxidative stress, inflammation, and endothelial dysfunction.70 Furthermore, the IDF contends that implementation of strategies to lower post-meal BG in those with post-meal hyperglycemia is important, but at this point, only low glycemic load diets and medications have been investigated as potentially effective strategies.

MITIGATING THE GLYCEMIC EFFECT OF FOOD WITH EXERCISE

In order to decrease inflammation and AGEs, limitation of high glycemic index foods in the diet would be ideal; however, implementation of this is difficult. Since some people may be unwilling or unable to limit their consumption of high GI foods, alternative means of blunting the BG spike of high glycemic index foods would be useful. Post-meal exercise may be one method for attenuating the BG increase associated with such foods. Glucose is a primary fuel for exercise and is used preferentially before fat stores are mobilized.44 Insulin is necessary to stimulate the translocation of the GLUT4 glucose transport protein from inside the cell to the cell surface in order for glucose to enter a muscle cell in the rested state. Exercise stimulates the translocation of GLUT4 transport proteins without insulin, facilitating glucose uptake from the blood into cells.48 Exercise plus insulin has an additive effect to some degree in the facilitation of glucose uptake by muscle cells. Previous research has shown that cycling (30 minutes at 70% maximum heart rate) blunts the BG spike after consumption of cornflakes (1 gm carbohydrate per kg body weight),29 and another study30 indicated that slow post-meal walking reduced the BG response to a meal of cornflakes (1 gm carbohydrate per kg body weight). Recent research determined that 30 min of light exercise (walking) reduced the blood glucose spike following consumption of a Milky Way candy bar, a typical snack, compared to the spike in BG that occurred when subjects sat after consuming the candy bar.52

The aforementioned studies were conducted with healthy subjects. In addition, Manohar and colleagues35 found that light activity after meals blunted the glycemic response to meals in both healthy individuals and those with type 1 diabetes (the less common, but more severe type of diabetes in which the pancreas produces no insulin). Studies examining the effect of post-meal exercise on the glycemic response to a meal in those with pre-diabetes and T2DM have garnered similar results. A recent study indicated that short bouts of exercise after meals improved the 24hr glucose control (measured via continuous BG monitoring) in older individuals at high risk for impaired glucose tolerance (pre-diabetes).56 Colberg and colleagues examined the effect of 20 min of moderate walking before or after meal consumption in individuals with T2DM.57 They found that post-meal exercise resulted in lower plasma glucose levels at the end of exercise compared to values at the same time point when subjects had walked pre-meal. Additional studies found post-meal exercise (1 hour moderate exercise58 or a short bout of intense exercise59 resulted in reduced hyperglycemia in those with T2DM; however, the exercise did not commence immediately after meal consumption. Additionally, subjects with higher pre-exercise BG levels in both studies benefited the most from post-meal exercise.

Although avoiding spikes in BG is important for people without diabetes, it is especially important for those with diabetes. It is well recognized that exercise in general improves insulin sensitivity50 and can improve glycemic control (indicated by HbA1c) in people with type 2 diabetes.71 HbA1c provides an indication of average BG levels over the previous 2-3 months. However, this test does not indicate if BG levels were relatively stable over that period of time, which would be ideal, or if the individuals experienced frequent peaks and valleys, which would be an unhealthy pattern. Mitigating spikes in BG after consumption of snacks and meals in people with diabetes could improve glycemic control, decrease the need for medication (or decrease the dosages needed), and delay the onset of the long term complications of diabetes. Further, facilitating stable levels of glucose in adults diagnosed with dementia through regular light exercise, particularly after meals, may positively affect mood and behavior, important aspects of dementia management, as well as physical health.72

CONCLUSION

Obese individuals, with or without cognitive impairment, are at risk for insulin resistance and T2DM. Post-meal hyperglycemia often precedes clinical diagnosis of the disease. Further, elevated BG in a person without diabetes may have adverse health consequences, as a diet high in refined carbohydrates and simple sugars is associated with increased accumulation of AGEs and greater levels of inflammatory markers. To date, the primary strategies to attenuate the spike in BG after a carbohydrate load have been low glycemic load diets and medication. However, low glycemic load diets can be difficult for many to adhere to, and avoidance of simple and refined carbohydrates at all times is not realistic for most. Thus, one approach to mitigate the post-meal spike in blood glucose after a carbohydrate load may be exercise commencing after consumption. Much additional research is needed to clarify the effect of post-meal exercise on the glycemic response to a carbohydrate load, including studies that examine different types, durations, and intensities of exercise, and studies that include obese subjects at-risk for insulin resistance as well as those with T2DM. In addition, the effect of mitigating the spike in BG after carbohydrate consumption on health outcomes needs to be further assessed. In a pivotal recent paper, Norton and colleagues75 documented that up to one-third of Alzheimer-type dementia may be attributed to potentially-modifiable risk factors such as the prevention of obesity, vascular disease, and diabetes and stressed the importance of physical exercise. If post-meal exercise does prove to effectively blunt the BG spike after a meal, it could be a low-cost...
convenient method to prevent the damaging consequences of elevated BG.

CONFLICTS OF INTERESTS

Both authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. No funding sources were involved in the development of this article.

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AUTHOR’S CONTRIBUTIONS

Associate Professor Heiss conceptualized and synthesized this review. Dr. Goldberg contributed her knowledge of issues in adults with dementia and contributed to the synthesis of the manuscript.

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