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The Role of Vitamin D in the Incidence of Metabolic Syndrome in Undergraduate Female Students in Saudi Arabia

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Running title: Vitamin D Deficiency and Metabolic syndrome among Saudi Obese young females

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Abstract: Background: *Vitamin D insufficiency/deficiency prevalent in all age groups across the world is common in obesity and may play an important role in the risk factors of metabolic syndrome (MS).* ***Objectives:*** *This cross-sectional study is to evaluate the relationship between levels of adiponectin and circulating 25(OH)D, and its effect on metabolic biomarker among overweight/obese female students.* ***Methods:*** *Three hundred female students; with mean age 20.9 ± 3.2 years were attending the Aljouf University, Sakaka, Saudi Arabia. They were randomly selected from university during the studying year 2015 – 2016. Anthropometric and biochemical indices were determined.* ***Results:*** *The study showed 19% of the female's student were either overweight or obese (15% and 4%, respectively). The frequency of MS diagnosis among the students was 17%, with 13% and 4% had either three or four risk factors, respectively. Overweight/obese subjects had significantly worse anthropometric and biochemical characteristics, including waist/hip ratio, blood pressure (BP), fasting blood glucose (BG), insulin, insulin resistance (HOMA-IR), triglyceride levels (TG), low-density lipoprotein cholesterol levels (LDL-C), leptin, adiponectin, leptin/adiponectin ratio and high-density lipoprotein cholesterol levels (HDL-C) compared to normal weight. Of the subjects diagnosed with MS, 59% had mild and 8.6% had severe 25(OH)D deficiency. There was negative association between 25(OH)D and both FBG and HOMA-IR among young women obese/overweight.* ***Conclusion:*** *In our study, it suggested that low level of adiponectin was strongly correlated with low 25(OH)D levels. Also, the prevalence of MS tends to increase with high occurrence rate of low circulating 25(OH)D levels that is, known cause poor glycemic control and prediction of cardiovascular outcomes.*

Keywords: Vitamin D deficiency, adiponectin, leptin, blood glucose, insulin resistance and lipid profile

1. INTRODUCTION

Vitamin D insufficiency/deficiency is prevalent in all age groups across the world. Vitamin D deficiency, which is deemed to occur at a low level of 25(OH)D in blood less than 50 mmol/l, is common in obese people[1]. Several studies have found serum 25(OH)D levels greater than 50 nmol/l to be prevalent (in up to 90% of the population) with partial of < 25 nmol/l in South Asia, Middle East and North Africa[1]. Low vitamin D status which indicated by circulating 25(OH)D is linked to metabolic risk factors such as inflammation, adipokines, insulin resistance, abnormalities of lipid profile, and high (BP) in adults[2]. However, many studies have evaluated the relationship between 25(OH)D concentrations and metabolic components in children and adolescents. Some workers suggested that vitamin D is isolated in excess fatty tissue, resulting in lack of biological availability[3]. In a study of Pittas et al., found that individuals who suffered from CVD were more vitamin D deficient than those without CVD[4]. In a different study that followed young adults for more than 20 years, vitamin D level, in combination with vitamin D supplementation, was inversely related to the incidence of MS in the study population [5]. It also, suggested that lifestyle factors and having high levels of body fat mass might contribute to this development. Kayaniyil et al., reported 25(OH)D levels to be negatively correlated with the first and second phases of insulin secretion, and to be positively correlated with insulin sensitivity in type-2 diabetes[6].

Adipokines secretes by adipose tissue, has a vital role on body weight, blood glucose, and lipid metabolism. Adiponectin, a collagen-like protein has anti-inflammatory, antiatherogenic and antidiabetic properties. Increased circulating of adiponectin is linked with reduced risk of impaired glucose tolerance, decreased myocardial infarction risk, and was suggest as indicator of atherosclerosis early [7]. In obesity, Adiponectin was declined and may be involved in type-2 diabetes and cardiovascular disease pathology [7]. Adipose tissues secrete leptin, a cytokine-like molecule that regulates the fatty mass and body weight by inhibiting eating and stimulating energy consumption [8]. Leptin was increases in obesity, type-2 diabetes, MS and

hypertension. Several studies have found that leptin is a biomarker of obesity, IR, MS and cardiovascular disease in adult[8].

Hyperlipidaemia, which considered to be an independent CVD risk factor, forms a potential link between low vitamin D levels and CVD. Dyslipidaemia, known to be a disorder of lipoprotein metabolism, is the result of excess TG, TC, LDL-C, and is due to the suppression of HDL-C. A favourable serum lipid profile is correlated with high levels of 25(OH)D which regulates the appropriate use of apolipoprotein A-1 (ApoA1), since it is a component of HDL Salehpou et al.,[9] conducted a study on obese individuals who received vitamin D supplement (25µg/d); the results of this study suggested that significantly elevated levels of HDL-C and Apo A-1 lowered body fat in obese individuals. The objective of the current study was to evaluate the relationship between levels of adiponectin and circulating 25(OH)D levels, and its effect on metabolic biomarker among overweight/obese female students who attending in Aljouf University, Sakaka, Saudi Arabia.

2. METHODS

Subjects

This cross-sectional study, which took place between November 2015 and June 2016, was performed on group of 300 overweight/obese female students; with mean age 20.9±3.2 years. Subjects were selected randomly from female students attended in Al Jouf University, Sakaka, Saudi Arabia. They were excluded from the following criteria: liver disease, kidney disease, diabetes mellitus, use of any medication that could affect bone health or vitamin D status within the previous three years, history of pregnancy, lactation convulsions, thyroid-parathyroid diseases, adrenal disease, or gonadal disease. All participates gave their informed consent before inclusion in this study. The study was approved by the Medical Research Ethics Committee of the Faculty of Medicine, King Saud University**.**

Data collection. Each subject completed a self-reporting questionnaire that revealed their socio-economic status, age, smoking habits, meal and snack frequencies, and level of physical activity, as well as the educational and occupational status of each of their parents **.**

Dietary data. For each subject, the following data were recorded: the frequency of meals and snacks, and daily intake of vegetables, fruits, fatty foods, sugars, milk, mushrooms, fish, and crustaceans. Lifestyle practices, such as physical activity (exercise) and history of vitamin D supplements, were also recorded**.**

Nutrient analysis. Daily dietary intake was recorded over three consecutive days to insure energy and nutrient intake. A software program, purchased from ESHA[10], was used to analyse the nutritional content of each subject's diet. The dietary reference intakes (DRI), which are the recommended dietary intakes for a healthy diet, were calculated for each subject, adjusting for local practices, gender, age, weight, height, and physical activity levels[11]

Anthropometric measurements. Anthropometric data, including weight and height, were recorded (to the nearest0.1kg and0.5cm, respectively) using a beam balance scale (Adam Equipment Inc.,USA) after removal of outer garments and shoes; body mass index (BMI) was calculated (body weight/kg/(body height/ m)2)[12]. Body weight was categorised according to BMI values using the National Institutes of Health guidelines: (i) normal with BMI range 18.5-24.9, (ii) overweight with BMI range 25.0-29.9, and (iii) obese with BMI > 30[13]. Waist and hip circumferences(cm) were measured and the weight-to-hip ratio(WHR) was calculated[14]. Systolic and diastolic blood pressures were recorded, using the average of two measurements that were taken within 15-minuts interval using standardised mercury sphygmomanometer. Subjects whose BP measurements were ≥130/85mmHg were classified as being hypertensive[15].

Diagnostic criteria. MS was diagnosed when three or more of the following criteria: abdominal obesity (WC≥88 cm), elevated FBG (≥ 100 mg/dl or diagnosed with diabetes, or taking an oral hypoglycaemic or insulin medication), reduced HDL-C level (≤40 mg/dl), elevated TG level (≥150mg/dl) and elevated BP (SBP≥130 mmHg, DBP≥85 mmHg or taking antihypertensive medication)[16].

Biochemical analyses. Blood samples were drawn after fasting for more than 12-hrs and the serum was separated and frozen at -20°C. Glucose concentration was estimated using a commercially available glucose kit (Randox Laboratories Ltd., UK.) based on the glucose oxidase method. Serum TC, LDL-C, HDL-C and TG, creatinine, uric acid, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were estimated colorimetrically using the available kits (cited in Randox Laboratories Ltd., UK). Serum 25(OH)D and insulin levels were measured by enzyme-linked immunosorbent assay (ELISA) (IDS, Tyne and Wear, UK). The inter- and intra-assay variabilities for 25(OH)D were 5.2% and 4.3%, respectively, and the inter- and intra-assay variabilities for insulin were 5.7%, and 3.1%, respectively. Insulin resistance was calculated using HOMA-IR (insulin[mU/L] ×glucose[mg/dl]/405[17]. Serum adiponectin and leptin were measured by ELISA. the intra-assay and inter-assay coefficients of variation for adiponectin was 5.4% and 8.5% respectively and intra-assay and inter-assay coefficients of variation for leptin was 7.4% and 9.3% respectively (Ani Biotech Oy, Orgenium Laboratories Division, Vantaa, Finland). The reading was taken using an ELISA microplate reader (VERSA Max, Molecular Devices Corporation, MN, USA). Vitamin D status was classified as follows: (i) deficient (vitamin D levels < 20 ng/ml), (ii) insufficient (vitamin D levels in the range 20 – 29 ng/ml), and (iii) sufficient (vitamin D levels >30 ng/ml)[18].

Statistical Analysis.

Data were expressed as mean ± standard deviation(SD) and data were analysed using SPSS version 12.0 software (SPSS, Chicago, III), using the appropriate statistical tests (chi-square

test, Student's t-test, correlation coefficient, odds ratio). The P values were considered significant for $P < 0.05$.

3. RESULTS

Socio-demographic characteristics of the study group are described in Table 1. The mean age of the subjects was 20.9 ± 3.2 years. The parents of the subjects had been educated to at least University standard in 66% (fathers) and 36% (mothers) of the cases. Most fathers (65%) were employed whereas few mothers (29%) were employed. Family history of MS was 64%**.** The study showed 19% of the subjects were either overweight/obese (15% and 4%, respectively). The frequency of MS diagnosis of the subjects was 17%, with 13% and 4% of the subjects having three or four risk factors, respectively (Table 2).

Anthropometric and biochemical characteristics of the subjects are detailed in Table 3. When compared to normal weight subjects, overweight\obese subjects had statistically significant of anthropometric and biochemical parameters. A higher levels of fasting blood glucose, insulin, HOMA-IR, leptin, leptin/adiponectin ratio, TG, LDL-C, W/H ratio, SBP and DBP in overweight/obese female students; but lower adiponectin and HDL-C levels. Also, overweight/obese subjects had significantly lower levels of 25(OH)D ($p<0.01$) relative to the normal weight.

Fifty-nine percent of the students that were diagnosed as having MS had mild 25(OH)D deficiency and 8.56% had severe 25(OH)D deficiency (Table 5). Serum 25(OH)D levels were negatively associated with BMI, FBG, leptin, leptin/adiponectin ratio, LDL-C, TG and BP, and positively associated with adiponectin and HDL-C ($P<0.01$) (Table 6). In addition, MS had pronounced impact on elevating leptin and inhibition adiponectin levels that was additive to overweight/obesity. Otherwise, leptin/adiponectin ratio, that had postulated as a biomarker, was increased in subjects with MS than without.

Table 7 details the association between MS and different risk factors. It can be observed that the primary predisposing risk factor for MS was abdominal obesity (OR 5.92). The second predisposing risk factor for MS was abdominal obesity, as indicated by WC (OR 5.26), followed by leptin (OR 4.84), Leptin/adiponectin ratio (OR 4.73), adiponectin (4.26), hypertension (OR 4.11), low HDL-C (OR 3.42), FBG (OR 3.11) and vitamin 25(OH)D (OR 2.87).

The levels of carbohydrates and sugar consumption were significantly higher in subjects with MS compared to those without (Table 8). Consumption of dietary saturated fats were significantly more by subjects with MS than those without, but dietary fibre was consumed significantly less among subjects with MS than those without.

In overweight/obese, the daily dietary intake of vitamin D was 198±136.6 IU/day and in normal weight was 190±129.6 IU/day. The intake of vitamin D as a percental of DRI was 101.0±69.2% in overweight/obese subjects and 89.9±49.8% in normal subjects. Among the groups study, no statistically significant in vitamin D intake was showed either based on daily intake or on the percent of DRI.

4. DISCUSSION

Vitamin D has a vital role of public health and human well-beings and its deficiency has been linked to several metabolic disorders including Cancer, autoimmune diseases, obesity, type-2 diabetes, hypertension and cardiovascular disease and there is a relationship between low serum 25(OH)D, HOMA-IR, type-2 diabetes and low adiponectin in adults[19]. In the finding Leptin was increased and adiponectin decreased in overweight/obese female students relative to normal weight**.** There was a strong correlation between leptin with abdominal obesity and inverse to adiponectin. Furthermore, leptin, leptin-to-adiponectin ratio and adiponectin were strongly correlated with MS. These results had additive effects to overweight/obesity among female students. The most important outcomes are the combination of risk factors with increased leptin or lack of adiponectin that was found in overweight/obesity among female students. A cross-sectional study by lee et al., conducted on adolescents aged 12–19 years showed that abdominal obesity was the predominate risk factor for IR and there is an inverse correlation between adiponectin and obesity and IR which is linked to risk factors of cardiac disease[20].

The results of our study showed that low serum 25(OH)D associated with abdominal obesity, adiponectin, HOMA-IR as well as leptin/adiponectin ratio. Leptin and adiponectin have adverse effects on inflammation and insulin resistance, the high level of leptin increases the expression of pro-inflammatory and vasoconstrictive factors[21]; while adiponectin stimulates anti-inflammatory cytokines production and enhanced the sensitivity of peripheral insulin[22]. Al-Daghri et al., observed that a positive correlation between BMI and; 25(OH)D and adiponectin in type-2 diabetes. The fact is that these adipokines has a potential role as a link between 25(OH)D and IR[23].

The current study showed 25(OH)D levels to be significantly lower in subjects who had been diagnosed with MS compared to those without MS. The finding also, observed that subjects who had been diagnosed with MS were mildly 25(OH)D deficient more frequently than those without. Additionally, vitamin D deficiency was more prevalent in obese subjects who had been diagnosed with MS(60.9%) compared to obese subjects without (33.3%). Previous studies have elucidated an inverse association between serum 25(OH)D levels and MS[24]. A cross-sectional study of 101 healthy subjects living in urban areas found a risk of MS increases three-fold in subjects with low levels of vitamin D (23.37% vs. 8.3% $P<0.001$)[24].

Interestingly, after ameliorating lifestyle intervention in children obese /adults, adiponectin is the most predictive indicator for improving metabolic disorder, while changes in leptin were not related to positive metabolic outcomes[25]. However, the clustering of many unfavorable biomarkers

strongly requires early intervention not only in childhood obesity, but also in normal weight of subjects whose feature appear the risk.

The underlying mechanisms of the association between 25(OH)D status and dyslipidaemia are poorly understood. Previous studies have demonstrated that being either overweight/ obese was strongly associated with dyslipidaemia (elevated TG and lower HDL-C) in Asian-Indian adolescents living in urban area[26]. In the third National Health and Nutrition Examination Survey[26], adults whose 25(OH)D level was in the lowest quartile had the highest risk of elevated serum TG levels (≥150 mg/dl); this demonstrates that the health dangers of low vitamin D levels. Similarly, in obese subjects, 25(OH)D levels below 50 nmol/l were associated with lower HDL-C and high TG levels[27]. In the present study, it was observed that the level of 25(OH)D was positively correlated with HDL-C ($P<0.01$) and negatively correlated with TG levels and LDL-C ($P<0.05$). The female students in our study who had been diagnosed with MS had significantly elevated levels of TC, LDL-C, TG and BP, and significantly reduced levels of HDL-C compared to those without MS. Several epidemiological studies found that serum 25(OH)D levels to be negatively associated with BMI[28,29]; excessive weight is a major component of MS, which may be attributed to lower 25(OH)D levels. However, in a cross-sectional study conducted on children, it was found that there is a negative correlation between 25(OH)D and BMI, FBG, LDL-C and TG, and positive correlation with HDL-C ($P<0.01$)[29].

Insulin resistance is strongly associated with obesity and type-2 diabetes, hypertension, hyperlipidaemia and CVD[30]. There is evidence from both clinical and non-clinical studies that glucose homeostasis might affect the level of vitamin D[30]. In pervious study that focussed on pancreatic β-cells and the effect of vitamin D receptors, it was found that glucose intolerance, impaired synthesis and secretion of insulin, as well as an increased risk of type-2 diabetes, may be affected by insufficient 25(OH)D levels[31]. Peterson et al., found that vitamin D deficiency is associated with different metabolic disorders, and the authors concluded that low levels of vitamin D is a risk factor for MS[31]. Our findings illustrated that significant increased odds ratio between high levels of TC, TG and LDL-C in subjects that had serum 25(OH)D levels below 20 ng/ml when compared to subjects that had normal serum 25(OH)D levels. The lower levels of 25(OH)D may be attributed to poor dietary intake of vitamin D as well as insufficient exposure to sunlight, despite the strong natural light of Saudi Arabia.

Considering the associations between MS and different predisposing factors, the finding found that obesity was the strongest predisposing risk factor for MS (OR:5.92). The second strongest predisposing risk factor for MS was abdominal obesity (OR:4.26). Unsurprisingly, WC, which is typically used as a surrogate measure of abdominal obesity, is the main criteria when determining MS risk. We also, found that the hypertension to be a strong risk factor for MS (OR:4.11); this similar with a study by Co et al who reported that hypertension (SBP & DBP) was the strongest predisposing risk factor with MS [32]. Previous studies of children living in urban areas have demonstrated that obesity is a major risk factor in the development of childhood hypertension[33]. In addition, we found that lifestyle is a risk factor for MS, with OR of 2.87. previous scientists indicated that regular physical activity and eating healthy diet have positive influence on health status, reducing the risk of obesity and thus reducing the risk of cardiac disease[29]. While elevated blood lipid levels increase the risk of hypertension, increasing physical activity lowers that risk; this is because exercise increases energy requirements and decreases fat deposition[34]. Bombak [35] found the prevalence of obesity to be increased by eating calorie dense food and failing to take adequate exercise While MS can be treated, in part, pharmacologically, the most important strategy for reducing the risk of MS and heart disease is to make lifestyle changes that promote physical activity and reduce excess weight.

An analyses of macronutrients showed that the consumption of carbohydrates and sugar were significantly higher in subjects with MS compared to those without MS, Whereas subjects with MS consumed less dietary fibre than without MS. Rapid changes in contemporary lifestyle habits can be seen in Saudi Arabia that are contributing to (i) increased consumption of foods that are high in carbohydrates and sugars, and (ii) lack of adequate physical activity; the combined result of these lifestyle changes is an increase the prevalence of MS in the Saudi Arabian population[36]. These results are consistent with studies that found sedentary lifestyle and poor dietary habits to be important predictors for development of MS[36].

5. CONCLUSION

In our study, it suggested that low level of adiponectin was strongly correlated with low 25(OH)D levels. Also, the prevalence of MS tends to increase with the high occurrence rate of low circulating 25(OH)D levels that is, known cause poor glycemic control. This relationship is unclear and may be a sign of future prediction of cardiovascular outcomes. Further studies are needed in the young population who are overweight/obese to assess the relationship between circulating adiponectin levels, low 25(OH)D and IR for adverse cardiovascular and metabolic outcomes. We suggest requiring strategies efforts to prevent the tendency of deficiency and should be improved in early and middle age by increasing outdoor physical activity and by strengthening dietary vitamin D in the diet part of the Saudi diet.

6. DISCLOSURE STATEMENT

The authors report that they have no conflicts of interest.

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