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Leptinemia among Obese Omani Adults Newly Diagnosed with Type 2 Diabetes Mellitus: A Case-control Study

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Leptinemia is associated with obesity and obesity and hyperinsulinemia are considered as the main etiological factors for type 2 diabetes mellitus (T2DM) among adult subjects. The present case-control study evaluated the dietary pattern and biochemical profile of newly diagnosed T2DM obese Omani adults as compared to their age, weight and gender matched control subjects. Two hundred Omani adults (100 obese adults newly diagnosed with T2DM and 100 healthy controls) were included in this study. Dietary intake, body mass index and biochemical measurements for fasting serum glucose, insulin, leptin and blood glycated hemoglobin levels were evaluated for all study participants. Subjects with T2DM showed significantly ($p<0.05$) higher daily intake of total fats, carbohydrates and energy as compared to controls. Leptinemia and hyperinsulinemia were common among obese diabetic adults as compared to controls. The mean fasting serum levels of glucose and glycated hemoglobin in obese diabetic subjects were significantly ($p<0.05$) higher than controls. Serum leptin level was found to be positively correlated with body mass index, serum insulin level and total energy intake in all the study subjects. Our results suggest that leptinemia is a risk factor for T2DM in obese Omani adults.

Key words: Dietary pattern, obesity, type 2 diabetes mellitus, leptin, Omani adults

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by chronic hyperglycemia associated with a disturbance of carbohydrate, fat and protein metabolism resulting from a defect in insulin secretion or action (Samuel and Shulman, 2012). Sedentary lifestyle, obesity and genetic predisposition synergize for the global epidemic of T2DM (American Diabetes Association, 2006). Leptin is an adipocyte-secreted hormone that plays a key role in regulating the pathophysiology of energy homeostasis, appetite and obesity (Brennan and Mantzoros, 2006). Leptinemia is common among obese subjects and serum reflects the amount of energy stored in adipose tissue (Wauters *et al*., 2000).

Leptinemia is thought to induce a hyperleptinemic state (leptin resistance) among obese subjects and it is debatable if obese diabetic adults are resistant to the effects of leptin in a similar way as the insulin resistance (Mantzoros *et al*., 2011; Tasaka *et al*., 1997). The ethnic differences in relation to serum leptin level have also been reported, as the Peruvian and Chilean Indians showed lower serum leptin levels comparing to the Caucasian population (Perez-Bravo *et al*., 1998; Lindgarde *et al*., 2001). Mexican Americans have also been reported to have higher serum leptin levels as compared to non-Hispanic Whites (Wei *et al*., 1997).

Leptinemia is associated with adiposity in pre-diabetic adults (Al-Daghari *et al*., 2006) and the differences in the adiposity features have been observed between the Asians, Caucasians and other ethnic groups (Thorpe *et al*., 2009). It has been suggested that obesity, leptin and insulin resistance are endogenous factors that might be involved in the etiology of T2DM among susceptible subjects in a pattern that is different in the Asians versus Asian-American population (Chan *et al*., 2009; McBean *et al*., 2004).

The Sultanate of Oman has a Middle-Eastern lifestyle with distinct dietary consumption patterns and is ethnically and culturally different from the Western countries. There is an accelerated increase in the incidence of T2DM among Omani adults and T2DM was more prevalent in urban areas than in rural population and accounted for 12% increase of all newly diagnosed non-communicable diseases in 2010 (Al-Riyami, 2010; Al-Moosa *et al*., 2006). There is no reported data with regard to the assessment of serum leptin levels in obese Omani adults diagnosed with T2DM. Therefore, we conducted this case-control study to evaluate the dietary consumption pattern and leptinemia in normal healthy and newly diagnosed obese Omani adults.

MATERIALS AND METHODS

Study subjects and setting: One hundred Omani adults (newly diagnosed with T2DM) and one hundred matched controls, non-diabetic normal healthy subjects, were evaluated from 1st June 2009 to end of June 2010 in the Outpatient Diabetes Clinic of Sultan Qaboos University Hospital (SQUH), a tertiary referral hospital and the principal governmental center for T2DM care in Oman. The study protocol was approved by the Medical Research and Ethical Committee of the College of Medicine and Health Sciences, Sultan Qaboos University.

Inclusion criteria: All participants were recruited on voluntary basis and signed an informed consent for the enrollment in the study. Inclusion criteria were: (1) Non-smokers and non-alcoholics; (2) Free of any endocrine disorders and non-communicable diseases; (3) Females were neither pregnant nor lactating; (4) Not receiving any vitamins or nutritional supplements. One hundred cases (50 male and 50 female subjects) participated in the study. They were all newly diagnosed with T2DM and did not receive any anti-diabetic medication. The controls (non-diabetic normal healthy subjects) were randomly selected from those accompanying the patients or attending the outpatient departments at the SQUH. The controls were matched with patients based on their age (±5 years), gender ratio and body weight (±5 kg). Personal interviews were scheduled for all study participants for completing the study questionnaire.

Anthropometric assessment: Anthropometric measurements (height, weight and body mass index, BMI) were estimated for all study subjects.

Dietary intake: Dietary assessment was estimated for all study participants. The retrospective dietary intake of the study participants was estimated using a semi-quantitative Food Frequency Questionnaire (FFQ), to assess their usual dietary intake over the previous 6 months (Block *et al*., 1990). The portion sizes were determined according to the commonly used household serving units/measures in Oman. The FFQ was tested for its validity, reliability and reproducibility before conducting the study. The FFQ included 9 different food groups (breads/cereals, vegetables, fruits, meat/meat substitutes, milk/dairy products, deserts, beverages, sandwiches and traditional Omani dishes). The collected dietary intake data was categorized into: (1) Frequency of food consumption: the number of daily servings of food groups, based on the frequency of consumption for all the respondents was subsequently grouped according to Food Guide Pyramid (Van Dijk *et al*., 2012) and (2) the daily intake of macronutrients. The Food Processor software version 10.2 (ESHA Research, Salem, OR, USA) was used to calculate the means of daily nutrient intakes (total energy intake, protein, fats and carbohydrates).

Biochemical measurements: The fasting blood samples were collected at the Outpatient's Clinic of SQUH. They were used for measurements of serum insulin, leptin and glycated hemoglobin (HbA1c). The diagnosis of T2DM was confirmed based on Their Fasting Serum Glucose (FSG) values (>7.0 mmol L^{-1}).

Statistical analysis: Data is expressed as Mean±SD (standard deviation) and was analyzed using The GraphPad Prism statistical software package for personal computer, version 5. Chi-square (χ^2) test was used for comparing the categorical variables. One way analysis of variance (ANOVA) followed by Tukey's test, Student's unpaired t-test, correlation coefficients (r) and the stepwise logistic regression analysis were used for comparing the continuous variables. The $p<0.05$ was considered as statistically significant.

RESULTS

The general characteristics of the enrolled study participants are presented in Table 1. Overweight and obesity were prevalent in patients with T2DM and similar pattern was observed in controls. No significant ($p>0.05$) differences were however observed in the Body Mass Index (BMI) of both the cases and controls. Almost 80% of the cases indicated a family history of T2DM, whereas only 12-16% of the controls had a family history of T2DM. The average mean Fasting Serum Glucose (FSG) values in T2DM patients (11.88±0.75 mmol L^{-1}) were significantly ($p<0.05$) higher as compared to controls (5.16±0.56 mmol L^{-1}). Similarly the average mean glycated hemoglobin (HbA1c) values in T2DM patients (11.3±2.2%) were significantly ($p<0.05$) higher as compared to controls (5.1±0.6%). The mean fasting serum insulin and leptin levels were found to be significantly higher in T2DM patients as compared to controls, t = 11.26 and t = 5.39, respectively, $p<0.05$ (Fig. 1a and b). In both cases and controls, the serum leptin level was found to be positively correlated ($p<0.05$) with BMI (r = 0.695 and r = 0.799, respectively), serum insulin level (r = 0.368 and r = 0.820, respectively) and total energy intake (r = 0.308 and r = 0.312, respectively).

Table 2 presented the daily servings from different food groups by the study participants, according to USDA Food Guide Pyramid and data showed no significant ($p>0.05$) differences with regard to the consumption of foods from cereals, meat and meat alternates and milk and milk products groups between the cases and controls. The consumption of fruits and

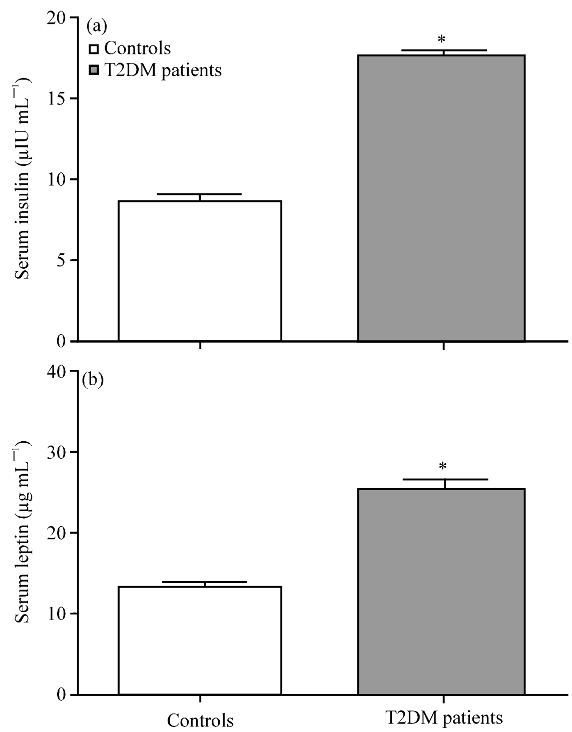

Fig. 1(a-b): (a) Hyperinsulinemia and (b) Leptinemia among T2DM patients and controls

Table 1:General characteristics of type 2 diabetic patients and controls

Characteristics	T2DM patients (N = 100) No.	%	Controls (N = 100) No.	%	p-value
Doing routine exercise	18	36.0	31	62.0	0.02*
Family history of type 2 DM	39	78.0	7	14.0	0.01*
Age in years (mean)	51.4	7.93	48.9	6.0	0.083
Monthly family income in Omani riyals (mean)	550	36.5	565	24.6	0.966
Body mass index (kg m^{-2})	30.5	2.8	28.2	3.9	0.39
Fasting serum glucose (FSG) (mmol L^{-1})	11.9±3.9		5.2±2.1		0.01*
HbA1c (%)	11.3±2.2		5.1±0.6		0.01*

Results are expressed as Means±SD, *p<0.05

Table 2: Food consumption frequency in patients with T2DM and controls

Food group (servings day^{-1})	T2DM patients (N = 100) No.	%	Controls (N = 100) No.	%	p-value
Bread, cereal, rice and pasta					
<6	13	26	8	16	0.47
6-11	25	50	28	56	
= 11	12	24	14	28	
Vegetables					
<3	35	70	12	24	0.01*
3-5	10	20	23	46	
= 5	5	10	15	30	
Fruits					
<2	14	28	5	10	0.03*
2-4	30	60	40	80	
>4	6	12	5	10	
Milk, yogurt and cheese					
<2	7	14	6	12	0.57
2-3	40	80	38	76	
= 3	3	6	6	12	
Meat, poultry, fish					
<2	9	18	4	8	0.10
2-3	27	54	37	74	
= 3	14	28	9	18	

Results are expressed as Means±SD, *p<0.05

Table 3: Average daily macronutrients intake in patients with T2DM and controls

Nutrient	T2DM patients (N = 100) Mean	SD	Controls (N = 100) Mean	SD	p-value
Protein (g day^{-1})	76.0	5.5	74.2	5.8	0.11
Total Fat (g day^{-1})	81.7	7.5	60.1	9.3	0.02*
Carbohydrates (g day^{-1})	409.6	82.1	360.7	68.5	0.001*
Total Energy intake (Kcal)	2677.7	118.4	2279.5	110.3	0.001*

Results are expressed as Means±SD, *p<0.05

vegetables was however significantly ($p<0.05$) higher in controls as compared to T2DM patients. The majority (70%) of T2DM patients consumed <3 daily servings of vegetables as compared to controls (24%).

The data on the average daily macronutrients and energy intake for the study participants is presented in Table 3. The mean daily intake of carbohydrates and fats (g day^{-1}) was significantly ($p<0.05$) higher in T2DM patients as compared to controls. No significant differences were however observed in the daily intake of proteins (g day^{-1}) between the cases and controls. The average daily total energy intake (kcal/day) was also significantly ($p<0.05$) higher in T2DM patients as compared to controls.

The model presented in Table 4 shows the association between the intake of various food items and the risk of type-2 diabetes mellitus. These associations were determined using the stepwise logistic regression analysis, where the dependent variables were either the T2DM patients or the controls. The results indicated that the total fats, saturated fats, sweets and cakes, red meat and potatoes were the main dietary factors associated with the risk of T2DM among these study participants. The vegetables and dairy products appeared to be the marginally independent predictors.

Table 4: The association of type 2 DM with different categories of food

Independent predictors	Adjusted OR	95% CI	p-value
Total fat	1.46	(1.15, 1.84)	0.02*
Saturated fats	2.66	(1.83, 3.88)	0.01*
Sweets and cakes	2.33	(1.67, 3.25)	0.01*
Red meat	1.80	(1.26, 2.58)	0.01*
Potato	1.77	(1.18, 2.66)	0.06*
Green leafy vegetable	0.99	(0.99, 1.00)	0.02*
Vegetables	0.99	(0.99, 0.99)	0.01*
Dairy products	0.89	(0.84, 0.94)	0.01*

*p<0.05

DISCUSSION

Our results are the first set of data from Oman that report about the dietary consumption patterns and their association with the fasting serum glucose, insulin, leptin and blood glycated hemoglobin levels in normal healthy and newly diagnosed type-2 diabetic obese Omani adults. In the present study, the mean serum leptin levels were significantly higher in T2DM patients as compared to controls. The serum leptin levels were found to be positively correlated with BMI, serum insulin and total energy intake in both the cases and controls. This indicates a direct positive correlation between the serum leptin and insulin levels, which is known to promote the adipogenesis and in turn can be involved in the pathogenesis of T2DM, this is in agreement with the data from several previous studies, which reported that the elevated leptin level is a risk factor in the development of T2DM, in particular in obese diabetic patients (Schmitz *et al*., 1997).

Leptin and ghrelin, both released from adipose tissues, modulate the insulin and glucose metabolism but exert antagonistic effects as the leptin acts to decrease the appetite and food intake (Zigman *et al*., 2006).

Leptin crosses the blood-brain barriers through a transport system and acts on the receptors through the lateral and medial regions of the hypothalamus to suppress the food intake and stimulate energy expenditure to regulate the appetite and energy balance (Konukoglu *et al*., 2006). Leptin has also a direct effect on insulin release through effects on α-cell function (Date *et al*., 2002). Obese subjects become leptin resistant through a chronic low grade pro-inflammatory state and high levels of leptin may adversely affect the functioning of α-cells and eventually can lead to the development of diabetes (Hukshorn *et al*., 2004).

Overweight and obesity were prevalent in our study participants as indicated from high BMI, which was positively correlated with high serum leptin levels that have also been shown to be directly correlated with total energy intake. Only a few population-based studies conducted in the Middle-East have reported an increased consumption of energy-dense high fat and sugar rich fast foods and decreased intake of fresh vegetables and fruits and their association in the development of type-2 diabetes mellitus and other non-communicable chronic diseases in the local population (Musaiger and Miladi, 1997; Galal, 2003).

In the Sultanate of Oman, the T2DM patients were accounted for 12% of all the newly diagnosed non-communicable diseases in 2010 (Al-Riyami, 2010). Recently it was reported that the quality of type-2 diabetes management as indicated by the 3 major intermediate outcome measures (glycemic control, blood pressure and lipid profile) in the Gulf Cooperation Council (GCC) was sub-optimal and relatively poor (Alhyas *et al*., 2011).

In the present study, high daily intakes of carbohydrates, fats and total energy were prominent among T2DM patients and were significantly ($p<0.05$) higher than that of control subjects. The quality of carbohydrates is an important dietary pattern, which emphasizes that low glycemic index and glycemic load foods may help to reduce the body weight and may improve the inflammatory and adipokine profiles in overweight and obese subjects (Neuhouser *et al*., 2011). It was also observed that higher intake of sweets and cakes were common among T2DM patients.

Our results are in line with the findings of previous studies, which reported that higher intake of simple carbohydrates was associated with hyperglycemia. The mean daily total fat intake in T2DM patients was significantly higher as compared to controls. The major sources of dietary fat were from the animal products mainly containing the saturated fats. The results of our study suggest that obesity and high daily intake of carbohydrates, fats and total energy are associated with increased risk of T2DM risk in Oman. Furthermore, our results are also in line with the data reported in recent studies, which showed that diets high in glycemic index, glycemic load and starch and low in fibre were associated with increased risk of diabetes (Bajorek and Morello, 2010; Sluijs *et al*., 2010). The average daily protein intake in T2DM patients and controls was comparable and was within the normal recommended proportionate percentage daily energy intake from proteins.

In this study, we observed that the patients with T2DM had low daily intake of fruits and vegetables, which may be associated with low daily intake of fiber. Fiber supplementation for T2DM patients can reduce the fasting blood glucose and HbA1c. This suggests that increasing dietary fiber in the diet of patients with type-2 diabetes is beneficial and should be encouraged as a disease management strategy (Post *et al*., 2012). Dietary fiber has also been reported to modulate the release of adipokines (adiponectin, leptin, tumor necrosis factor-α and interleukin-6) that can lead to a chronic sub-inflammatory state and may play a central role in the development of insulin resistance and T2DM leading to increased risk of CVD associated with obesity (Sanchez *et al*., 2012).

Significantly higher mean fasting serum glucose (FSG) levels and HbA1c values were observed in T2DM patients as compared to controls. Data suggests that the foods such as fruits, vegetable, whole grains and legumes, which are rich in dietary fiber, should be recommended for dietary management of T2DM as they are considered low glycemic index foods and can help to control the hyperglycemia in T2DM patients (Bajorek and Morello, 2010). Daily total vegetable intakes of 200 g or more and green vegetable intake of 70 g or more has been reported to be well correlated with improved control of HbA1c and triglyceride levels in elderly type 2 diabetes patients through achieving a well-balanced diet (Takahashi *et al*., 2012).

CONCLUSION

In conclusion, our study suggests that dietary consumption patterns varied, in particular the intake of carbohydrate, fat and total energy was significantly higher in newly diagnosed T2DM patients as compared to controls. High serum leptin levels in T2DM patients were positively correlated with average daily total energy intake, BMI and serum insulin levels leading to insulin resistance that might be one of the triggers in the development of T2DM in Omani adults.

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