ORIGINAL ARTICLE

Leptin Levels in Obese and Non-Obese African and Caucasian Subjects With Type 2 Diabetes

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It has previously been demonstrated that circulating levels of leptin show ethnic differences when controlled for the confounding influence of adiposity. This study examined leptin levels in non-obese and obese subjects with type 2 diabetes of African versus Caucasian origin.

Materials and Methods: Non-obese and obese subjects with type 2 diabetes of either African origin living in Dar es Salaam, Tanzania (n=22) or Caucasian origin living in Malmö, Sweden (n=24) were studied by taking a fasting sample for analysis of insulin and leptin after an overnight fast. All subjects were treated with metformin alone or with sulfonylurea with or without addition of metformin.

Results: It was found that age, BMI, waist circumference, blood pressure and fasting glucose or insulin did not differ between Africans and Caucasians, when divided into obese and non-obese subjects. However, leptin levels were 50% higher in the African subjects than in the Caucasians, when controlled for gender and BMI (P=0.01).

Conclusion: We conclude that both in non-obese and obese subjects with type 2 diabetes, leptin levels are higher among subjects of African origin than of Caucasian origin. This may be related to higher risk of cardiovascular diseases in these subjects.

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Key Words: Diabetes, Leptin, Obesity

Introduction

Leptin is a hormone produced by the adipocytes in proportion to degree of adiposity.[1] A main function of the hormone is to signal the size of the peripheral energy stores to the brain for proper adjustment, mainly inhibition of food intake and increase in energy expenditure when leptin levels are high.[1] Hyperleptinemia may, however, also be involved in the development of cardiovascular diseases, since it has been demonstrated that leptin independently associates with cardiovascular events.[2-4] This may be due to activation by leptin of the sympathetic activity, which is related to the increased blood pressure.[5-7] This may be of particular importance in subjects with. type 2 diabetes, in whom obesity contributes to increased burden of cardiovascular complications.[8] On the other hand, subjects with type 2 diabetes seem to have reduced leptin levels.[9,10]

It has recently been shown that leptin levels display ethnic differences. For example, a large population study from the United States has shown that leptin levels were higher in non-Hispanic blacks than in non-Hispanic whites with subjects of Mexican American

origin having leptin levels in between.[11] Furthermore, Amerindian subjects living in Peru have lower leptin levels than Caucasians from Sweden[12] and low leptin levels are also observed in Amerindians from Paraguay.[13] Also, subjects living at the pacific island of Kitava have lower leptin levels than Caucasians, [14] whereas subjects of south Asian origins seem to have higher leptin levels than subjects of Caucasian or Chinese origin.[15,16] In subjects of African origin, the information is not conclusive since studies with higher leptin than other ethnic groups[11] or no difference[17-18] have been published.

To further explore whether differences exist in leptin levels in subjects of African origin versus other subjects, we have compared the leptin levels in non-obese and obese subjects with type 2 diabetes of African origin living in Dar es Salaam, Tanzania, with those obtained from similar groups of subjects in Caucasians living in Sweden.

Materials and Methods

The study included 22 African patients from Abbas Medical Center, Dar es Salaam, Tanzania, and 24 Caucasian patients from the Department of Medicine, Malmö, Sweden. Study subjects were consecutive patients attending Abbas Medical Center or, in Malmö, invited to take part in the study as a part of Malmö Preventive Medicine Studies. Patients were excluded if they had evidence of type 1 diabetes, diabetes resulting from pancreatic injury, secondary forms of diabetes, a history of acute metabolic diabetic complications, significant diabetic or other clinically relevant conditions (for example, asthma, myocardial infarction). Eight patients used lipid-reducing agents. Of invited patients, response rate was 72%. All participating subjects had type 2 diabetes and were treated with metformin alone (n=7), sulfonylureas alone (n=23) or sulfonylurea in combination with metformin (n=16). They were all well controlled as judged by fasting glucose levels <8 mmol/l; HbA1c levels were not available in subjects from Dar es Salaam; in the Malmö population the range of HbA1c levels were 5.7 to 7.1% (reference value<5.3%). Following an overnight fast, the subjects attended the clinic, before the oral hypoglycemic agents were taken. A fasting blood sample for determination of glucose, insulin and leptin was obtained. The study was approved by the Ethics committé at Lund University and by authorities at Muhimbili Medical Center, Dar es Salaam, Tanzania.

Samples were taken in tubes with EDTA and immediately centrifuged. Plasma was separated and frozen at -20°C until analyzed. Samples taken in Dar es Salaam were transported to Sweden for analysis. Plasma levels of insulin and leptin were analysed with radioimmunoassay kits (Linco Res., St Charles, Mo, USA). Free and bound radioactivity were separated by use of an anti-IgG (goat anti-guinea pig) antibody. The sensitivity of the insulin assay is 17 pmol/L and the coefficiency of variation (CV) is less than 3% at both low and high levels; sensitivity of the leptin assay is 0.5 ng/mL and the CV is less than 8%. Glucose was analysed with the glucose oxidase method. In addition, at the patients visit, age and duration of diabetes, systolic and diastolic pressure, body mass index and waist circumference were measured.

Statistical analyses were performed by calculating the leptin levels for each of the four groups (males/females and non-obese/obese) in percent of the mean of leptin levels for the particular subgroup in the African subjects. Two-way ANOVA with Bonferroni post-hoc analysis was then applied for test of significance between African versus Caucasian subjects with each group (obese or non-obese), as stated. No stratification for treatment was applied.

Results

Table 1 and 2 show the results in the eight groups of subjects, divided into males (Table 1) and females (Table 2). When comparing African patients with Caucasian patients, age, duration of diabetes and blood pressure did not differ between the groups, and, similarly,

fasting glucose values also were not different between the groups. BMI and waist circumference were higher in obese than in non-obese subjects in both males and females ($p<0.01$). Fasting insulin was higher in obese than in non-obese subjects ($p<0.05$ or less). These are all expected values in these patient groups, and show no ethnic differences. Leptin levels were, as expected, higher in obese than in non-obese subjects ($p<0.001$). When comparing insulin and leptin levels in African versus Caucasian subjects, insulin levels did not differ. On the contrary, leptin levels were higher in African subjects. This was evident by calculating the mean of the leptin levels in the four different groups of subjects as percentage of the mean of that particular subgroup among African subjects for each gender. These values were then 104±14% (±SEM) in African subjects versus 66.5±2.8% in Caucasians ($P=0.010$). Hence, across all subjects, leptin levels were approximately 50% higher in African subjects. There were no differences in leptin levels, depending on treatment (metformin alone, sulfonylurea alone or sulfonylurea plus metformin).

Table 1. Characteristics of non-obese and obese male subjects included in this study

	Non-obese males		Obese males	
	Africans (n=7)	**Caucasians (n=6)**	**Africans (n=5)**	**Caucasians (n=6)**
Age (yrs)	52.4 (14.6)	55.4 (10.6)	51.2 (7.9)	57.2 (4.9)
Duration (yrs)	7.2 (4.8)	5.2 (2.8)	5.2 (4.9)	3.2 (2.9)
BMI (kg/m^2)	22.1 (1.1)	23.1 (1.8)	34.6 (3.5)*	32.6 (1.5)*
Waist circumference (cm)	75.8 (4.8)	86.8 (4.9)	108.7 (5.7)*	118.7 (4.7)*
Systolic BP (mmHg)	133 (20)	125 (10)	138 (20)	129 (18)
Diastolic BP (mmHg)	86 (6)	79 (6)	87 (8)	78 (9)
Fasting glucose (mmol/l)	6.7 (3.9)	6.3 (2.9)	6.5 (1.7)	6.9 (2.1)
Fasting insulin (pmol/l)	38 (17)	58 (17)	53 (17)*	83 (21)*
Leptin (ng/l)	5.3 (4.9)	3.8 (1.0)	18.5 (7.6)*	14.1 (1.9)*

Numbers represent mean (SD).
* $p<0.05$ compared with the same ethnicity non-obese subjects

Table 2. Characteristics of non-obese and obese female subjects included in this study

	Non-obese females		Obese females	
	Africans (n=4)	**Caucasians (n=6)**	**Africans (n=6)**	**Caucasians (n=6)**
Age (yrs)	50.0 (14.9)	54.0 (6.9)	55.1 (13.9)	59.1(8.9)
Duration (yrs)	6.2 (5.8)	4.2 (3.8)	6.0 (5.1)	5.0 (3.1)
BMI (kg/m^2)	20.6 (1.1)	23.8 (0.9)	35.1 (4.4)*	32.1 (2.4)*
Waist circumference (cm)	72.5 (3.8)	78.5 (6.8)	109.6 (15.1)*	102.6 (8.1)*
Systolic BP (mmHg)	131 (23)	120 (16)	136 (28)	124 (21)
Diastolic BP (mmHg)	78 (12)	72 (15)	82 (6)	78 (9)
Fasting glucose (mmol/l)	6.5 (2.5)	6.6 (1.8)	7.5 (1.2)	7.2 (1.1)
Fasting insulin (pmol/l)	41 (16)	51 (12)	56 (17)	86 (22)*
Leptin (ng/l)	7.8 (4.2)	4.6 (0.4)	18.1 (6.4)*	10.7 (1.9)*

Numbers represent mean (SD).
* $p<0.05$ compared with the same ethnicity non-obese subjects

Discussion

This study shows that leptin levels were higher in African subjects with type 2 diabetes living in Dar es Salaam, compared with Caucasian patients living in Sweden in spite of no significant differences in adiposity, as judged from values of BMI and waist circumference, or in insulin levels. Hence, ethnic differences exist in leptin levels between African and Cuacasian non-obese and obese subjects with type 2 diabetes.

Previous studies have shown that ethnic differences exist in leptin levels.[10-16] Thus, leptin levels were higher in non-Hispanic blacks than in non-Hispanic whites in a study in the United States[11] and Amerindian subjects living in Peru have lower leptin levels than Caucasians from Sweden.[12] Also, subjects living at the pacific island of Kitava have lower leptin levels than Caucasians, [14] whereas subjects of south Asian origins seem to have higher leptin levels than subjects of Caucasian or Chinese origin.[15,16] In subjects of African origin, studies with higher leptin than other ethnic groups[11] or no difference[17,18] have been published. We show here that diabetic subjects of African origin have higher leptin levels than subjects of Caucasian origin. We show, furthermore, this to be the case both in non-obese and obese subjects.

The reason for the higher leptin levels in diabetic subjects of African origin is not clear. It may reflect different body composition, although in our study, BMI and waist circumference did not differ between the groups. However, differences in regional distribution of adiposity may exist as previously has been observed in that different metabolic risks due to different body compositions exist between black and white people in spite of similar BMI.[19] It should also be emphasized that judging adiposity by BMI or waist circumference limits conclusions on regional distribution of adipose tissue. The difference in leptin could also be related to differences in insulin levels or insulin sensitivity, because insulin stimulates the expression of leptin.[1] However, this explanation is not likely to explain the ethnic difference in the present study, because there was no significant difference between the groups in basal glucose and insulin; if anything, insulin levels tended to be lower in African subjects. It may, finally, also be speculated that genetic differences in expression rate of leptin explain the difference.

A consequence of the difference would be increased risk of disorders associated with the metabolic syndrome in the African subjects, since leptin has been shown to be associated with such disorders.[2-4] However, whether increased risk of complications is evident in African patients is not established. It has been suggested that whereas the degree of microvascular complications is higher in African patients than in patients of other ethnic origins, the degree of macrovascular complications is lower.[20,21] Further studies are required to examine the incidence of complications in these patients, and the potential role of leptin for development of these complications.

A limitation of the study is the small sample size; hence it is not clear how the finding in the present study relate to the entire population. Therefore, further studies are recommended, on larger numbers of subjects. In conclusion, leptin levels are higher in African subjects with type 2 diabetes living in Dar es Salaam in Tanzania than in Caucasians living in Malmö in Sweden. This suggests that leptin levels display an ethnic difference.

Acknowledgements

The authors are grateful to the patients who participated in the study and to the medical and nursing staff at the centers for their assistance.Special thanks also to Lilian Bengtsson, Lund University, for expert technical assistance in the analysis and to Alfiya Esmail, AbbasMedicalCenter, for excellent secretarial assistance. This study was supported by the Swedish Research Council (Grant 6834), The Swedish Diabetes Foundation, Albert Påhlsson Foundation, and the Faculty of Medicine, Lund University.

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