Microalbuminuria and adiponectin in obese nondiabetic nonhypertensive people

Mohamed I. Atta, Nilly H. Abdalla, Ahmed A. Ibrahim

Department of Internal Medicine, Faculty of Medicine, Beni Suef University, Beni Suef city, Egypt

Correspondence to Nilly H. Abdalla, MD, Lecturer of Internal Medicine, 59 Elkolifa Arg Soultan Elminia, Elminia-Egypt
e-mail: nillyhelmy@yahoo.com

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Introduction
The prevalence of obesity has increased dramatically over the last decade. The first sign of renal injury is microalbuminuria or frank proteinuria. The prevalence of microalbuminuria was positively increased with the increasing waist-to-hip ratio in nonhypertensive individuals. Adiponectin plays a role in the suppression of metabolic derangements that may result in diabetes, obesity, and nonalcoholic fatty liver disease and an independent risk factor for metabolic syndrome.

Aim
The aim of the study was to evaluate the relationship between obesity, adiponectin level, and microalbuminuria in obese nondiabetic nonhypertensive individuals.

Patients and methods
This study included 70 individuals who were divided into two groups according to their BMI: the obese group (group I), which included 50 people with BMI at least 30 kg/m^2, and the control group (group II), which included 20 lean persons with BMI from 18.5 to 24.9 kg/m^2. The study excluded patients with diabetes, hypertension, and chronic kidney disease. The following laboratory investigations were carried out on all subjects: serum glucose level, kidney function tests, and serum adiponectin level. Spot urine samples were collected for complete urinanalysis and tested for microalbuminuria and albumin/creatinine ratio (ACR).

Results
ACR showed significant increase in the obese group than in the nonobese group, but serum adiponectin showed significantly lower level in the obese group than in the nonobese group. Within the obese group a significant positive correlation was found between ACR and BMI and waist-to-hip ratio, whereas a significant negative correlation was found between ACR and serum adiponectin. Also, within the obese group a significant negative correlation was found between serum adiponectin level and ACR and BMI.

Discussion and conclusion
Through this study we have confirmed the association of microalbuminuria, obesity, and serum adiponectin. Our study supports the hypothesis that obesity is associated with microalbuminuria in obese people free from diabetes, hypertension, and chronic kidney disease.

Keywords:
adiponectin, microalbuminuria, obesity

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Introduction and aim of the work

The worldwide prevalence of obesity has increased dramatically over the last several decades. In the USA alone, over 60% of adults 20–74 years of age are now considered overweight or obese [1]. There is an increasing epidemic of obesity in the USA and worldwide [2]. BMI has been used to screen obesity. BMI equals a person's weight in kg divided by their height in meters squared (m^2) [3,4]. The incidence and prevalence of end-stage renal disease continues to grow steadily. Although much less common than obesity, end-stage renal disease is an important health problem because of the high cost of renal replacement therapy, the associated high mortality, and the effect on patients' quality of life [5]. The first sign of renal injury is microalbuminuria or frank proteinuria [6]. The prevalence of microalbuminuria was positively increased with the increasing waist-to-hip ratio (WHR) in nonhypertensive subjects [7]. Microalbuminuria is actually considered an ideal target for early prevention of the progression of kidney and vascular damage [8]. Adiponectin plays a role in the suppression of the metabolic derangements that may result in diabetes, obesity, atherosclerosis [9], and nonalcoholic fatty liver disease and is an independent risk factor for metabolic syndrome [10].

The aim of the study was to evaluate the relationship between obesity, adiponectin level, and microalbuminuria in obese nondiabetic, nonhypertensive subjects.

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Patients and methods

This study included 70 subjects (selected from the outpatient clinic of internal medicine department of Beni Suef University Hospital and Beni Suef general hospital). They were divided into two groups on the basis of their BMI: group I (the obese group) included 50 persons with BMI at least 30 kg/m^2, comprising 12 men and 38 women; their ages ranged between 24 and 56 years with a mean of 38.8 ± 8.9 years and their mean BMI was 37.5 ± 3.7 kg/m^2. Group II (the control group) included 20 lean persons with BMI from 18.5 to 24.9 kg/m^2, comprising 11 men and nine women; their ages ranged from 19 to 50 years with a mean of 35.5 ± 7.9 years and their mean BMI was 24.2 ± 2.6 kg/m^2. Exclusion criteria included having diabetes, hypertension, chronic kidney disease, and urinary tract infection. All participants in this study were subjected to the following: full history taking, complete clinical examination, and measurement of blood pressure with a standard sphygmomanometer. Three measurements were taken while the individual was seated and the lowest value was recorded. Anthropometric measurements included the following: triceps skin fold (TSF) thickness, measured using a Huidplooidikte meter (PhysioSupplies, Sylviuslaan 9, 9728 NS Groningen, The Netherlands) and according to the anthropometry normogram (above 23 mm in men and above 30 mm in women indicates obesity); height and weight, measured using a full-length stadiometer for height and the mass meter for weight; BMI [weight (kg)/(height (m^2)]: below 18.5 was considered underweight, 18.5–24.9 was considered normal, 25–29.9 was considered overweight (or preobese), and more than 30 was considered obese; WHR: waist circumference was measured using a tape at mid-distance between the bottom of the rib cage and the iliac crest, and hip circumference was measured opposite the gluteal region. WHR provided the index of relative accumulation of abdominal fat (normal in men below 0.9 and below 0.85 in women). Abdominal ultrasonography was performed to exclude renal diseases. Laboratory investigations included testing serum glucose levels using blood samples, kidney function tests, and serum level of adiponectin. Further, spot urine specimens were collected for complete urine analysis and tested for microalbuminuria [using urine albumin/creatinine ratio (ACR)], pyuria (microscopic), and hematuria (microscopic). Ten milliliters of venous blood were collected from each patient and control. Blood samples were transferred into clean dry tubes and allowed to clot, and serum samples were separated by centrifugation at 3000 rpm for 5 min. Each serum sample was divided into two clean dry tubes, one tube for estimation of random serum glucose, serum urea, and serum creatinine and the other tube for estimation of serum adiponectin. Random glucose and kidney function tests were performed immediately. Serum samples for estimation of adiponectin levels were stored frozen at 2–8°C for up to 3 months. Spot urine samples were collected in dry clean containers. From each urine sample a volume of 5 ml was centrifuged at 3000 rpm for about 10 min and about 1 ml of supernatant was taken by automatic pipette and transferred into a clean dry tube for estimation of microalbumin and creatinine. In alkaline solution creatinine forms an orange-red-colored complex with picric acid. The absorbance of this complex is proportional to the creatinine concentration in the sample. Then ACR is calculated by dividing microalbumin (mg/l) over creatinine (g/dl). If the ACR is 30–300 mg/g creatinine, micro albuminuria is diagnosed. Adiponectin (Acrp30) enzyme-linked immunosorbent assay is for quantitative detection of human adiponectin in cell culture supernatants, plasma, and human serum immunosorbent assay (ELISA) kit (Orgenium Laboratories, Vantaa Finland).

Statistical analysis

The data of all subjects were fed into an IBM-compatible computer, and SPSS (Quarry Bay, Hong Kong) for windows student version 16.0 was used to analyze these data. Data were expressed as mean ± SD for parametric variables and as numbers and percentage for nonparametric variables. Statistical analysis was conducted to evaluate the difference between groups under study as regards the various parameters using the Student *t*-test. Correlation between the essential studied parameters was determined by means of the Pearson correlation test. The Fisher Exact test is available only for 2 × 2 tables. It computes the exact probability under the null hypothesis of obtaining the current distribution of frequencies across cells, or one that is more uneven. The correlation coefficient (r) is a single number that describes the degree of relationship between two variables. A positive correlation coefficient means that as the value of one variable increases, the value of the other variable also increases, and as one decreases the other decreases. A negative correlation coefficient indicates that as one variable increases, the other decreases, and vice-versa. This was expressed as probability of value (P). The difference was considered significant if P value less than 0.05.

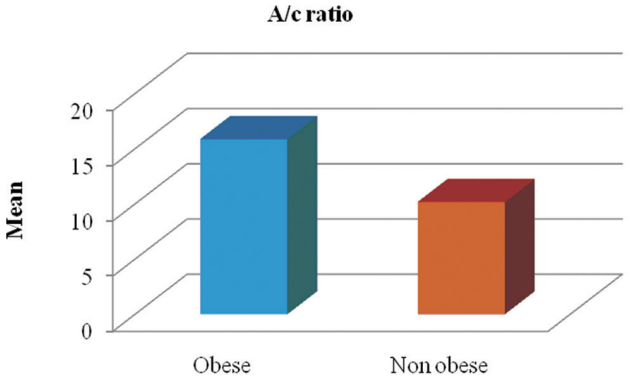
Results

The study included 70 nondiabetic nonhypertensive participants (selected from the outpatient clinic of the

internal medicine department of Beni Suef University Hospital and Beni Suef general hospital). They were divided into two groups on the basis of their BMI: group I (the obese group) included 50 persons with BMI at least 30 kg/m^2; their ages ranged between 24 and 56 years with a mean of 38.8 ± 8.9 years and their mean BMI was 37.5 ± 3.7 kg/m^2. Group II (the control group) included 20 lean persons with BMI from 18.5 to 24.9 kg/m^2; their ages ranged from 19 to 50 years with a mean of 35.5 ± 7.9 years and their mean BMI was 24.2 ± 2 kg/m^2. The two groups were matched as regards age, sex, and smoking history (Table 1 and Figs. 1, 2). The obese group had significantly higher body weight (P = 0.001), BMI (P = 0.001), TSF (P = 0.001), and WHR (P = 0.001), compared with the nonobese group. Also, no significant difference was detected between the two groups as regards random blood sugar (RBS), systolic blood pressure (SBP), diastolic blood pressure (DBP), blood urea, and serum creatinine (Table 1). ACR significantly increased in the obese group compared with the nonobese group (P = 0.008), but the obese group had significantly lower serum adiponectin level compared with the nonobese group (P = 0.008) (Table 2 and Figs. 3,4). Within the obese group, women had significantly higher ACR (P = 0.011) and BMI (P = 0.037) but significantly lower serum adiponectin (P = 0.025) compared with men (Table 3 and Fig. 5), because of the higher prevalence of obesity in women than in men.

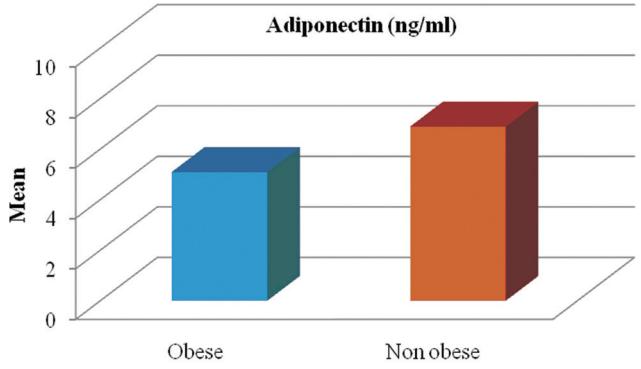
In the obese group significant positive correlation was found between ACR and BMI (r = 0.341; P = 0.030) and WHR (r = 0.470; P = 0.001) but significant negative correlation with serum adiponectin (r = −0.25; P = 0.049); however, there was no significant correlation between ACR and age, weight, height, TSF, RBS, SBP, DBP, urea, and creatinine (Table 4 and Figs. 6,7). In the obese group, significant negative correlation was found between serum adiponectin level and ACR (r = −0.25; P = 0.049) and BMI (r = −0.31; P = 0.029), but there was no significant correlation between serum adiponectin level and age, weight, height, TSF, WHR, RBS, SBP, DBP, urea, and creatinine (Table 5 and Fig. 8).

Figure 1



Comparison between obese and nonobese participants according to sex.

Figure 2



Comparison between obese and nonobese participants according to smoking.

Table 1: Demographic and laboratory data of both groups

	Mean±SD		*P*	Sig.
	Obese (*n*=50)	Non obese (*n*=20)		
Age (Year)	38.8±8.9	35.5±7.9	0.153	NS
Sex: Male\Female	15\35	11\9	0.060	NS
Smoking No\Yes	44\6	16\4	0.391	NS
Weight (Kg)	99.7±10.1	66.9±10.5	0.001	HS
Height (Cm)	163.8±5.6	165.3±7.3	0.388	NS
B.M.I (Kg/m^2)	37.5±3.7	24.2±2.6	0.001	HS
T.S.F.(mm)	40.1±5.7	18.8±3.9	0.001	HS
W.H.R.	1.2±0.2	0.8±0.1	0.001	HS
RBS (Mg/dl)	103.5±15.4	106.2±18.0	0.527	NS
SBP (mmHg)	123.6±8.8	121.5±8.8	0.368	NS
DBP (mmHg)	79.2±7.2	77.0±6.6	0.241	NS
Urea (Mg/dl)	34.4±6.1	36±5.1	36±5.1	NS
Creatinin (Mg/dl)	0.9±0.2	0.9±0.2	0.9	NS
Abd u/s Renal disorder	No	No	0.102	NS

Discussion

The worldwide prevalence of obesity has increased dramatically over the last several decades. Obesity is also a major worldwide public health problem. Microalbuminuria can detect early renal disease before progression of the condition to structural renal damage and frank macroalbuminuria [11]. However, few studies have examined the relationship between excess weight and risk for chronic renal disease [12]. Biopsy studies from humans have clearly established that obese patients have lesions that are distinct from diabetic nephropathy or hypertensive nephrosclerosis [13]. Adiponectin is a secretory protein expressed in adipocytes. The mechanism of regulation and expression is unknown. Adiponectin attenuates the endothelial inflammatory response by inhibiting the endothelial expression

Table 2: A/c ratio and S. Adiponectin level in both groups

	Obese (*n*=50)	Non obese (*n*=20)	*P*	Sig.
A/c ratio Mean±SD	15.9±8.8	10.2±5.1	0.008	HS
Adiponectin (ng/ml) Mean±SD	5.1±2.9	6.9±3.4	0.041	S

Table 3: Comparison between male and female according to A/c ratio, Adiponectin and BMI in Obese

	Mean±SD		*P*	Sig.
	Female	Male		
A/c ratio	16.3±4.8	12.3±5.3	0.011	S
Adiponectin (ng/ml)	5.1±2.2	6.5±1.2	0.025	S
BMI	38.9±4.7	36.2±3.5	0.037	S

Table 4: Correlation between A/c ratio and the following parameter in Obese

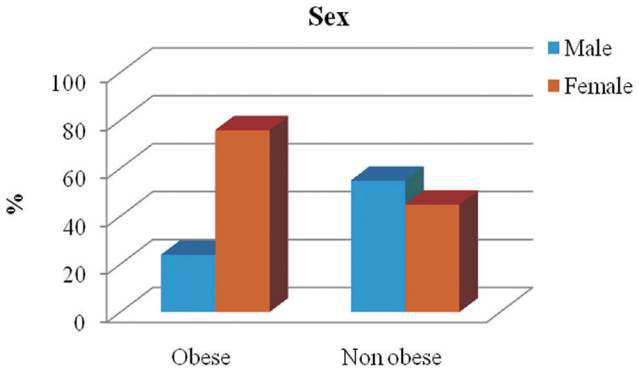
	r	*P*	Sig.
Age (Year)	0.109	0.451	NS
Weight (Kg)	0.067	0.644	NS
Height (Cm)	−0.089	0.539	NS
B.M.I (Kg/m^2)	0.341	0.030	S
T.S.F.(mm)	0.109	0.450	NS
W.H.R.	0.470	0.001	HS
RBS (Mg/dl)	0.083	0.569	NS
SBP (mmHg)	−0.202	0.159	NS
DBP (mmHg)	0.012	0.934	NS
Urea (Mg/dl)	0.153	0.287	NS
Creatinine (Mg/dl)	0.121	0.404	NS
Adiponectin (ng/ml)	−0.25	0.049	S

Table 5: Correlation between S.adiponectin (ng/ml) and the following parameter in Obese

	r	*P*	Sig.
Age (Year)	0.101	0.484	NS
Weight (Kg)	0.042	0.771	NS
Height (Cm)	0.057	0.695	NS
B.M.I (Kg/m^2)	−0.31	0.029	S
T.S.F.(mm)	0.132	0.360	NS
W.H.R.	−0.111	0.442	NS
RBS (Mg/dl)	0.011	0.942	NS
SBP (mmHg)	0.095	0.513	NS
DBP (mmHg)	0.215	0.134	NS
Urea (Mg/dl)	−0.107	0.461	NS
Creatinin (Mg/dl)	−0.247	0.084	NS
A/c ratio	−0.25	0.049	S

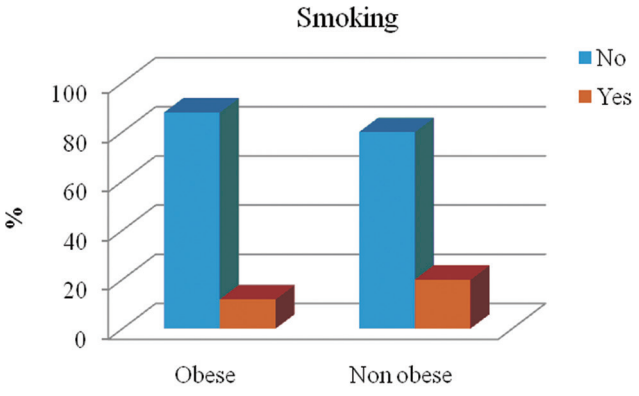
r: pearson correlation.

Figure 3



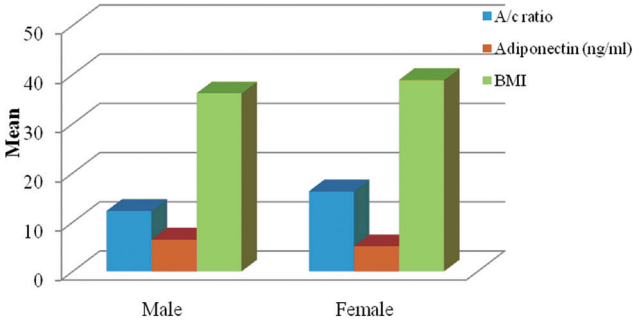
Comparison between obese and nonobese participants according to ACR. ACR, albumin/creatinine ratio.

Figure 4



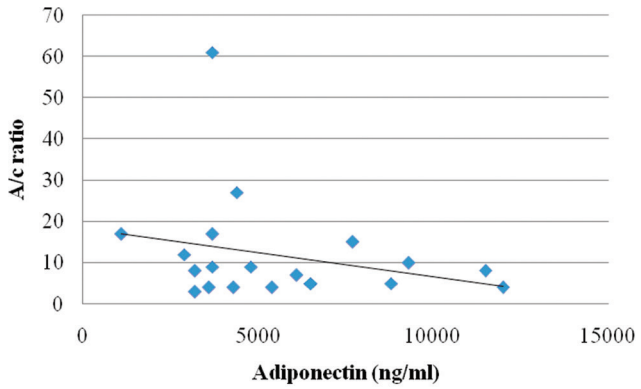
Comparison between obese and nonobese participants according to serum adiponectin.

Figure 5



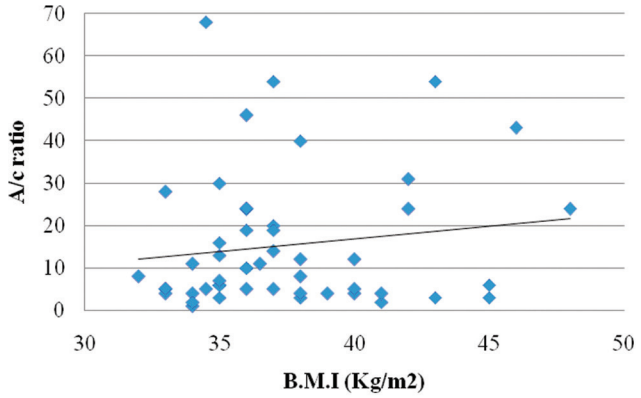
Comparison between men and women according to ACR, adiponectin, and BMI in the obese group. ACR, albumin/creatinine ratio.

Figure 6



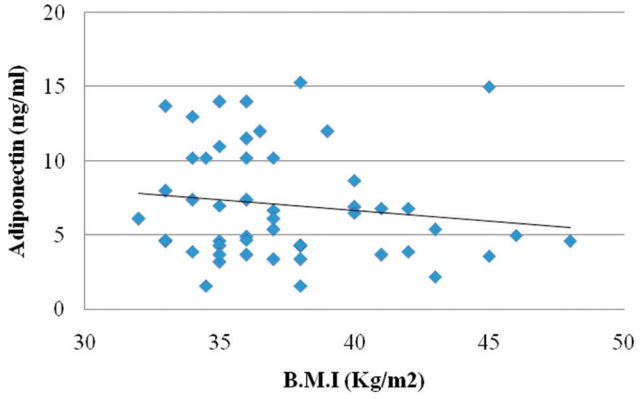
Correlation between ACR and adiponectin in the obese group. ACR, albumin/creatinine ratio.

Figure 7



Correlation between ACR and BMI in the obese group. ACR, albumin/creatinine ratio.

Figure 8



Correlation between adiponectin and BMI in the obese group.

of vascular cell and intercellular adhesion molecules and Eselectin, which are triggered by inflammatory cytokines. Plasma concentrations of adiponectin are low in obesity [14]. Our study supports an association between obesity, serum adiponectin, and the presence of albuminuria in adults after exclusion of diabetics and hypertensives because diabetes and hypertension are two well-established risk factors for chronic kidney disease. The important parameters assessed are BMI, WHR, TSF, serum adiponectin, ACR, and serum creatinine. In our study ACR was significantly higher in the obese group than in the nonobese group and ACR was positively correlated with BMI (P = 0.030). This indicates that higher BMI is a risk factor for the development of microalbuminuria in the obese group. Our findings are consistent with other reports that link higher BMI with albuminuria [15,16]. Also our results are consistent with published data from [17,18], who found that BMI remained a risk factor even after adjustment for baseline blood pressure and diabetes status. In the Coronary Artery Risk Development in Young Adults study [19] a U-shaped relation was observed between quartiles of BMI measured at year 10 and albumin excretion, independent of blood pressure and fasting glucose. One limitation of this study is that participants were enrolled in the 1970s and 1980s, well before the dramatic increase in obesity in the USA population that our study captures.

In a cross-sectional study, [20] found that the main determinants of microalbuminuria on the population level were increased age, obesity, and family history of hypertension and obesity; these factors had greater odds for microalbuminuria than did diabetes and hypertension. Most adipocytokines are positively correlated with obesity; however, adiponectin is negatively correlated with obesity and appears to be downregulated in more obese patients [21,22]. In our obese subjects, serum adiponectin was significantly lower than in nonobese subjects. This result is in agreement with [23], who found adiponectin levels to be lower in obese individuals than in lean individuals, despite increased adipose tissue mass. Also the clinical study of adiponectin was conducted by [24] to measure plasma levels of adiponectin in obese subjects; surprisingly, plasma adiponectin concentrations were lower in obese subjects than in nonobese subjects.

In this study, we searched for a correlation between ACR and other variables significantly associated with obesity in the obese group using Pearson's correlation to find a possible causation for the elevated ACR in obese healthy subjects. There was significant negative relation between ACR (P = 0.008) and serum adiponectin (P = 0.014). This result was in agreement with [25], who confirmed that plasma adiponectin concentration was inversely related to urinary albumin excretion in obese African Americans [26]. Also observed an inverse correlation between adiponectin level and albuminuria. Some reports link low adiponectin levels to microalbuminuria [27]. Demonstrated

a reduction in albuminuria and an increase in adiponectin after significant weight loss in the severely obese. This observation may refer to a relation between albuminuria and serum adiponectin [7]. Demonstrated that in nonhypertensive subjects the prevalence of microalbuminuria was positively increased with increasing WHR. Signs of early endothelial dysfunction manifested as microalbuminuria were strongly and independently associated with central obesity. Our results showed significant increase in BMI ($P = 0.001$), TSF ($P = 0.001$), and ACR in the obese group when compared with the nonobese 'control group'. WHR, which provides an index of a relative accumulation of abdominal fat, was found to be higher in the obese group than in the nonobese group. Also there was a strong positive correlation between WHR ($P = 0.001$) and ACR. These results are consistent with the results of [28], who determined that subjects with central fat distribution are at risk for renal function impairment and initiation of microalbuminuria independent of blood pressure and plasma glucose levels. In our study obese women had significantly higher ACR ($P = 0.011$) and BMI ($P = 0.037$) compared with obese men. However, women had significantly lower serum adiponectin ($P = 0.025$) than did men; on the contrary, [29] found that there was a positive correlation between serum adiponectin and the female sex. The reason for the association between adiponectin and low-grade albuminuria being detected only in the obese but not in nonobese persons was unclear, but several possible reasons are proposed by some experimental studies. [30] showed that there was no existence of adiponectin in the normal vascular walls in rabbits; however, marked attachment was detected in the balloon-injured vascular wall. These findings suggested that adiponectin might work protectively against the metabolic or vascular abnormalities from fat when its damage is still less severe, whereas it has no specific effects in the absence of such abnormalities.

Recommendations

(a) Follow-up study on obese subjects (without chronic kidney disease, diabetes mellitus (DM), or hypertension) is needed to determine the progression of microalbuminuria and its effect. (b) Weight loss should be encouraged in obese subjects (without chronic kidney disease, DM, or hypertension) to decrease microalbumiuria, which is considered a risk factor for chronic kidney disease. (c) Further prospective studies (with a large population and different races) are needed to re-examine the presence of independent relation between obesity and progression of chronic kidney disease.

Summary

Obesity is an excessive accumulation of energy in the form of body fat that impairs health. Obesity has reached epidemic proportions in developed countries and is rapidly increasing in many middle-income and less-developed countries. In European countries and the USA, obesity and overweight have been increasing for decades and constitute an epidemic that is a serious public health challenge and an important risk factor for morbidity and mortality [1]. Emerging evidence suggests that obesity may be independently related to kidney disease. For instance, animal studies have demonstrated that obesity *per se* can cause structural glomerular changes, whereas human studies have found that obesity is associated with increased renin–angiotensin system and sympathetic nervous activity, glomerular hyperperfusion and hyperfilteration, and an increased hazard ratio for incident microalbuminuria.

In this study, we hypothesized that obese healthy persons would show early evidence of kidney injury represented by microalbuminuria, and this microalbuminuria may be related to low adiponectin, which is associated with obesity. To address this question, we conducted a case–control study. A cohort of volunteers (without chronic kidney disease, DM, or hypertension) were selected from the outpatient clinic of internal medicine department of Beni Suef University Hospital and Beni Suef general hospital). These volunteers were divided into two groups according to BMI: 20 volunteers with BMI less than 30 kg/m^2 were included in the nonobese group and 50 volunteers with BMI more than 30 kg/m^2 were included in the obese group. Fasting blood samples were taken from all volunteers for measurement of serum creatinine, blood sugar, and serum adiponectin. A morning urine sample was collected from each volunteer, and microalbumin and urinary creatinine were measured. ACR was then calculated for every person. We then compared the two groups using parametric and nonparametric tests, and looked for a relation between ACR and different variables in obese subjects using Pearson's correlation. We have confirmed the association of microalbuminuria, obesity, and serum adiponectin. Our study supports the hypothesis that obesity is associated with microalbuminuria in obese subjects free of diabetes, hypertension, and chronic kidney disease.

Conclusion

Our study showed an inverse association between adiponectin and microalbuminuria independent of its metabolic or blood pressure effects in obese nondiabetic persons. Our results suggested the possibility that adiponectin plays a role as an endogenous protective factor against the development of albuminuria from obesity-related initial renal injury.

This was a hypothesis-generating survey, however, and longitudinal and intervention studies are needed to clarify our hypothesis.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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