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Adiponectin, total antioxidant status, and urine albumin excretion in the low-risk "Golden Years" type 1 diabetes mellitus cohort

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Abstract

Adiponectin is associated with inflammation and oxidative stress. Levels are reduced in type 2 diabetes mellitus and coronary heart disease. Conversely, levels are elevated in type 1 diabetes mellitus (T1DM) and associated with microalbuminuria and diabetic nephropathy. An explanation may be that elevated adiponectin in T1DM represents a beneficial counterregulatory response to disease. Our aim was to examine adiponectin in relation to urinary albumin excretion and plasma total antioxidant status (TAOS) in subjects with long-standing T1DM. Serum adiponectin and plasma TAOS were measured in 338 samples from the Golden Years cohort. These subjects have T1DM for at least 50 years and are at low risk of complications. Subjects were divided into normoalbuminuria, microalbuminuria, and macroalbuminuria groups. Adiponectin was elevated in women (20.53 ± 5.94 vs 11.8 ± 3.6 mg/L, $P < .001$); therefore, the samples were sex stratified. Within men, adiponectin was higher in those with macroalbuminuria (normoalbuminuria vs microalbuminuria vs macroalbuminuria: 10.97 ± 3.26 vs 11.55 ± 3.50 vs 23.63 ± 7.07 mg/L, $P = .002$). In women, no difference was observed (20.48 ± 5.61 vs 20.75 ± 7.04 vs 29.62 ± 7.81 mg/L, respectively; $P = .42$). Plasma TAOS did not differ by groups. The correlation between adiponectin and TAOS showed a linear increase from normoalbuminuria, microalbuminuria, to macroalbuminuria in men ($r = 0.33$, $P = .001$; $r = 0.48$, $P < .001$; $r = 0.59$, $P = .04$) and women ($r = 0.25$, $P = .01$; $r = 0.63$, $P < .001$; $r = 0.79$, $P = .08$). Adiponectin was higher in women. Within men, levels were significantly higher in the presence of macroalbuminuria. In both sexes, adiponectin and TAOS were correlated, which was most marked with micro-/macroalbuminuria. The increase in adiponectin in the face of an insult may be a compensatory mechanism to reduce oxidative burden.

1. Introduction

Adiponectin is an abundant protein secreted by adipocytes. Increased serum adiponectin is associated with higher all-cause mortality in patients with type 1 diabetes mellitus (T1DM) and coexisting nephropathy [1]. Furthermore, in T1DM, higher levels of adiponectin are associated with microalbuminuria [2,3], reduced glomerular filtration rate, overt nephropathy, and retinopathy [4]. Hypoadiponectinemia is associated with insulin resistance [5], endothelial dysfunction [6], obesity [7], type 2 diabetes mellitus (T2DM) [8], coronary heart disease (CHD) [9], and hypertension [10]. Furthermore, prospective studies have shown low levels to be predictive of the future risk of T2DM and myocardial infarction [9]. Therefore, there appears to be a paradoxical inverse association between plasma adiponectin and complication risk in patients with T1DM compared with T2DM.

Previous work suggests that adiponectin has anti-inflammatory and antiatherogenic properties and may influence oxidative stress [11-13]. Recent evidence suggests that a low level of adiponectin is associated with increased oxidative stress [14], and in vitro studies demonstrate that adiponectin may reduce oxidative stress [15,16]. This might explain the increase in cardiovascular risk associated with low levels of adiponectin. Of interest, an inverse correlation has been observed between urinary levels of 8-epi-prostaglandin $F_{2\alpha}$, a marker of oxidative stress, and blood levels of adiponectin in humans [17,18]. A possible explanation may be that elevated adiponectin in T1DM

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represents a beneficial counterregulatory response to disease, where circulating levels might increase in parallel with nephropathic progression to limit renal microvascular damage and inflammatory changes through its anti-inflammatory and antiatherogenic properties. A protective role for adiponectin in nephropathy is supported by animal models where adiponectin administered to adiponectin knockout mice has been observed to reverse urinary protein leakage through modulation of oxidative stress [19]. Further studies are required to investigate this. Of note, previous studies examining functional gene variants in the adiponectin gene have not shown conclusive associations with microvascular complications in T1DM [20-22]. In the prospective study by Jorsal et al [1], 2 single nucleotide polymorphisms in the adiponectin gene were associated with increased serum adiponectin; but these were not associated with renal or cardiovascular outcome. These findings might suggest that the increased levels of adiponectin in T1DM and nephropathy may be stimulated by renal insufficiency or alternatively result from a defect in the clearance of the protein as supported by the observation that successful kidney transplantation is followed by decreased plasma adiponectin concentrations [23]. Furthermore, patients with long-term renal graft survival are characterized by a higher plasma adiponectin concentration [24].

Our aim was to examine adiponectin in relation to urinary albumin excretion and plasma total antioxidant status (TAOS) in subjects with long-standing T1DM.

2. Methods

2.1. Subjects

Previous studies have demonstrated that patients with long-duration (>50 years) T1DM are relatively protected from clinical small- and large-vessel disease, as well as an absence of hypertension, having normal body weight and a low insulin dose [25,26]. The Golden Years project began in 1996 with the dual aim of (1) describing the clinical features of subjects with long-duration T1DM and (2) establishing a collection of DNA from this cohort. Patients with T1DM of long duration are awarded medals by Diabetes UK: the Alan Nabarro medal after 50 years and the RD Lawrence after 60 years of insulin treatment. Patients awarded medals between 1993 and 1996 were recruited [27]. The methods of study have been published previously [27]. In brief, after obtaining ethical approval and written consent from all medal holders and their consultants, research nurses visited the patients at home to collect clinical and biochemical data. The clinical information obtained was subsequently verified with patient records. This comprised a total of 400 subjects. Analysis was confined to subjects from the Golden Years cohort where plasma was available for analysis (340 had plasma TAOS measured, of whom 338 also had adiponectin concentrations measured). For this study, *microalbuminuria* was defined as an albumin-creatinine ratio greater than 2.5 mg/mmol in men and 3.5 mg/mmol in women [28-30]. *Macroalbuminuria* was defined as an albumin-creatinine ratio greater than 30 mg/mmol. Within the sample, urinary albumin data were available on 323 subjects (177 men and 146 women). Coronary heart disease status was defined by the presence of symptomatic or treated angina or hospitalization with a diagnosis of myocardial infarction. Estimated glomerular filtration rate (eGFR) was calculated using the Cockgroft-Gault formula.

2.2. Measurement of plasma TAOS

Plasma samples were stored at −80°C. Plasma TAOS, which is inversely related to oxidative stress, was measured by the modification of Sampson et al [31] of Laight's photometric microassay, using 2.5 μL of plasma in 96-well enzyme-linked immunosorbent assay plates. The TAOS of plasma was determined by its capacity to inhibit the peroxidase-mediated formation of the 2,2-azino-bis-3-ethylbensthiazoline-6-sulfonic acid radical. There are 2 arms to the assay: a control arm and test arm. In the control arm, phosphate-buffered saline is used instead of plasma. The difference in absorbance (control absorbance minus test absorbance) divided by the control absorbance (expressed as a percentage) was used to represent the percentage inhibition of the reaction. The inter- and intraassay coefficients of variation were 10.1% and 4.3%, respectively. Previously, we have shown that baseline plasma TAOS is associated with prospective risk and has a good correlation with plasma F_2-isoprostanes [32].

2.3. Measurement of serum adiponectin

All serum samples were kept at continuous −80°C since collection. The concentration of serum adiponectin was assayed using an enzyme-linked immunosorbent assay–based Quantikine Human Acrp30 immunoassay kit (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. The assay measures total (low, middle, and high molecular weight) adiponectin and uses a quantitative sandwich enzyme immunoassay technique to determine adiponectin concentrations. Standards over the range of 1 to 250 mg/L were prepared using recombinant human adiponectin. All serum samples were diluted according to the manufacturer's instructions. The intra- and interassay coefficients of variation are 2.8% to 4.1% and 0.1% to 3.5%, respectively.

2.4. Statistical analysis

Statistical analysis was performed using SPSS (version 10.1; SPSS, Chicago, IL). Results are presented as mean ± standard deviation. For data that had a normal distribution after log transformation, the geometric mean and approximate standard deviation are shown. These included serum adiponectin, high-density lipoprotein (HDL), and triglyceride. Plasma TAOS underwent a square root transformation

and is represented as median and interquartile range. For duration of diabetes, creatinine, and total daily insulin dose, the data could not be transformed to a normal distribution; and so, the data are expressed as median and interquartile range. Analysis of variance was used to assess the association between urinary albumin excretion groups and baseline characteristics for data with a normal distribution or after log/square root transformation. For duration of diabetes, creatinine, and total daily insulin dose, the data were analyzed by the Kruskal-Wallis test. The correlations between baseline parameters and adiponectin were tested by Pearson rank correlation coefficient for data with a normal distribution or by Spearman test for data that did not have a normal distribution (creatinine, duration of diabetes). Within this analysis, stepwise regression was initially performed to look for the final factors associated with adiponectin in men and women. χ^2 tests were used to compare differences in categorical variables by urinary albumin excretion groups. In all cases, a P value < .05 was considered statistically significant. Two-sided statistical testing was performed. Correction for multiple comparisons was not applied to the results because the study design was predominantly "hypothesis testing." Although making such an adjustment reduces the type I error, it leads to increases in the type II error; and fewer errors of interpretation occur when no adjustment is made [33].

3. Results

Serum adiponectin and TAOS were measured in 338 samples from the Golden Years cohort. Within the sample, no difference was observed in serum adiponectin by CHD status (no CHD vs CHD: 15.17 ± 5.17 vs 14.62 ± 4.78 mg/L, P = .74). Of interest, in this cohort, the only difference observed in risk factors by CHD status was in age (no CHD vs CHD: 68.7 ± 7.9 vs 71.2 ± 7.4 years, P = .03). Adiponectin was elevated in women (20.53 ± 5.94 vs 11.8 ± 3.6 mg/L, P < .001); therefore, the sample was sex stratified. In the whole sample, body mass index (BMI) differed by sex (women vs men: 24.0 ± 3.9 vs 25.3 ± 3.2 kg/m^2, P = .009).

The differences in baseline risk factors grouped by urinary albumin excretion are shown in Table 1. As observed in both sexes, the degree of albumin excretion was associated with glycemic control (hemoglobin A_{1c} [HbA_{1c}]). As may be seen in Fig. 1, within men, adiponectin was higher in those with macroalbuminuria (normoalbuminuria vs microalbuminuria vs macroalbuminuria: 10.97 ± 3.26 vs 11.55 ± 3.50 vs

Table 1
Clinical measurements grouped by urinary albumin excretion in men and women

Variable	Men			P	Women			P
	Normoalbuminuria	Microalbuminuria	Macroalbuminuria		Normoalbuminuria	Microalbuminuria	Macroalbuminuria	
	100	65	12		106	34	6	
Age (y)	69.0 (7.7)	70.0 (8.4)	67.6 (13.6)	.68	66.9 (9.5)	72.1 (8.4)	68.5 (14.5)	.03
Duration of diabetes (y)[a]	55 (52-57)	55 (53-58)	54 (52-66)	.61	54 (52-59)	55 (52-64)	54 (50-70)	.40
BMI (kg/m^2)	25.4 (3.2)	25.3 (3.4)	24.9(2.6)	.92	23.9 (3.8)	24.3 (4.3)	21.5 (2.8)	.43
W/H ratio	0.90 (0.06)	0.90 (0.06)	0.90 (0.07)	.51	0.81 (0.09)	0.82 (0.07)	0.82 (0.05)	.97
HbA_{1c} (%)	**7.2 (1.2)**	**7.9 (1.4)**	**8.6 (1.3)**	**<.001**	**7.5 (1.3)**	**7.9 (1.2)**	**9.0 (3.1)**	**.02**
Cholesterol (mmol/L)	**5.5 (1.0)**	**5.8 (1.1)**	**6.0 (1.1)**	**.03**	6.0 (1.0)	6.3 (1.3)	6.2 (1.3)	.51
HDL (mmol/L)[b]	1.7 (0.2)	1.6 (0.2)	1.5 (0.2)	.31	1.9 (0.2)	2.0 (0.3)	1.8 (0.3)	.64
Triglyceride (mmol/L)[b]	1.3 (0.3)	1.5 (0.3)	1.5 (0.2)	.12	1.2 (0.2)	1.2 (0.2)	2.0 (0.6)	.44
Adiponectin (mg/L)[b]	**10.97 (3.26)**	**11.55 (3.50)**	**23.63 (7.07)**	**.002**	20.48 (5.61)	20.75 (7.04)	29.62 (7.81)	.42
TAOS (%)[a]	52.4 (49.2-57.3)	52.5 (47.4-57.6)	54.5 (45.2-58.6)	.89	53.5 (50.5-56.9)	53.1 (46.6-57.1)	54.6 (52.0-56.9)	.59
Creatinine (μmol/L)[a]	**100.5 (90.3-109.8)**	**102.0 (88.0-120.5)**	**127 (111-205.3)**	**.005**	90 (79-103)	92 (80-111)	97 (91-145)	.22
Creatinine clearance (mL/min)	**66.0 (19.1)**	**62.9 (20.1)**	**33.6 (13.2)**	**.001**	49.4 (15.1)	47.4 (14.8)	43.1 (18.9)	.67
Insulin injections (1, 2, 3) %	8/74/18%	8/80/13%	0/100/0	.67	10/73/17%	18/55/27%	0/50/50%	.31
Total daily insulin dose (U)[a]	36 (30-48)	40 (30-51)	31 (26-39)	.28	28 (22-35)	27 (22-37)	26 (20-34)	.95
Current smoker (%)	17%	21%	0%	.46	7%	13%	0%	.54

Data are mean and standard deviation or geometric mean and approximate standard deviation for log-transformed data. Analysis was performed by analysis of variance after transformation of nonnormally distributed data and by Kruskal-Wallis for duration of diabetes, creatinine, total daily insulin dose. χ^2 test was used to compare groups. Significant associations are highlighted in bold. Within the sample, urinary albumin data were available on 323 subjects. W/H indicates waist to hip.

[a] Median and interquartile range are shown for duration of diabetes, TAOS, creatinine, and total daily insulin dose.

[b] Log-transformed data.

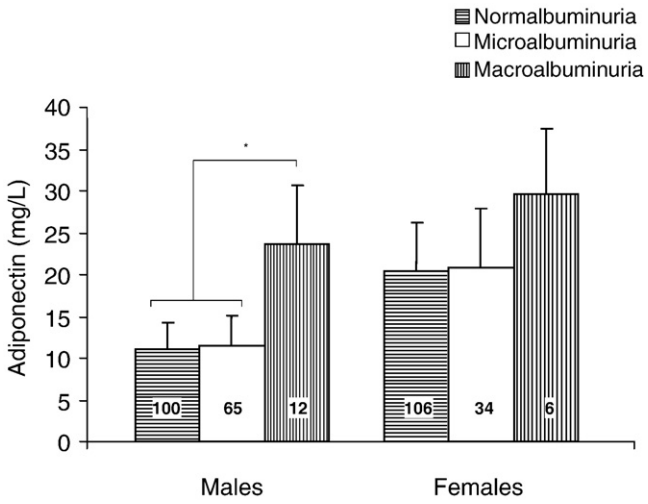

Fig. 1. Serum adiponectin grouped by sex and urinary albumin excretion. Geometric mean and approximate standard deviations. Numbers of subjects are shown at the base of each column. *$P < .01$ for normoalbuminuria/microalbuminuria vs macroalbuminuria in men. Within the sample, urinary albumin data were available on 323 subjects.

23.63 ± 7.07 mg/L, $P = .002$). In women, no difference was observed by groups (20.48 ± 5.61 vs 20.75 ± 7.04 vs 29.62 ± 7.81 mg/L, respectively; $P = .42$).

3.1. Serum adiponectin and correlation with plasma TAOS

Before stratification by urinary albumin status, in men, serum adiponectin was correlated positively with TAOS, HDL, and creatinine ($r = 0.39$, 0.35, and 0.37, respectively; all Ps < .01) and negatively with BMI and triglyceride ($r = -0.21$ and −0.34, respectively; $P < .05$). Stepwise backward regression showed that TAOS and triglyceride concentration were the strongest independent predictors of serum adiponectin (both Ps < .001). For the women, serum adiponectin was correlated positively with TAOS and HDL ($r = 0.36$ and 0.44, respectively; both Ps < .001) and negatively with triglyceride ($r = -0.40$, $P < .001$). Stepwise backward regression showed plasma TAOS and HDL again to be independent predictors of serum adiponectin (TAOS, $P = .02$; HDL, $P < .001$). Of note, as demonstrated in Table 1, no difference was observed between these variables by urinary albumin status.

Table 2 shows the correlation of serum adiponectin with baseline measurements grouped by urinary albumin status. Within the men, the correlation between serum adiponectin and TAOS increases across the spectrum of increasing urinary albumin excretion. A similar trend may be observed in women; however, the correlation between adiponectin and TAOS was not significant in the macroalbuminuric group ($r = 0.79$, $P = .08$) where the number of subjects was small. Of interest, correlations may also be observed with plasma triglyceride and HDL within the groups. Both of these variables are correlated with each other ($r = 0.38$ in men, $r = 0.31$ in women, $P < .001$) and are previously well recognized. Although we felt that sex stratification was important because of baseline difference in adiponectin between men and women, for men and women combined, the correlations between TAOS and adiponectin in the 3 groups were significant (normoalbuminuria: $r = 0.268$, $P < .001$; microalbuminuria: $r = 0.485$, $P < .001$, macroalbuminuria: $r = 0.62$, $P = .006$). Within men and women, before urinary albumin grouping, stepwise backward regression showed that the correlation between plasma TAOS and adiponectin was independent of the other variables including eGFR and creatinine.

4. Discussion

Previous studies have shown increased adiponectin to be associated with the development of microalbuminuria and

Table 2
Correlation of serum adiponectin with clinical variables grouped by urinary albumin excretion

Variable	Men			Women		
	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
	100	65	12	106	34	6
Age	**0.28, $P = .007$**	0.03, $P = .81$	−0.33, $P = .33$	0.09, $P = .38$	0.03, $P = .87$	0.30, $P = .57$
Triglyceride	**−0.28, $P = .004$**	**−0.50, $P < .001$**	**−0.57, .05**	**−0.36, <.001**	**−0.45, .008**	−0.74, $P = .10$
Creatinine[a]	**0.30, $P = .003$**	**0.34, $P = .007$**	0.24, $P = .44$	0.08, $P = .44$	−0.12, $P = .52$	0.49, $P = .33$
Creatinine clearance	**−0.37, $P = .03$**	**−0.54, $P < .001$**	−0.11, $P = .83$	−0.08, $P = .55$	−0.49, $P = .02$	0.75, $P = .25$
BMI	**−0.28, $P = .03$**	−0.16, $P = .31$	0.32, $P = .54$	−0.22, $P = .09$	−0.20, $P = .37$	0.66, $P = .35$
W/H ratio	−0.24, $P = .05$	−0.12, $P = .45$	−0.57, $P = .24$	0.08, $P = .54$	−0.24, $P = .29$	−0.25, $P = .75$
HDL	**0.37, $P < .001$**	**0.48, $P < .001$**	**0.02, $P = .96$**	**0.40, $P < .001$**	**0.54, $P = .01$**	0.17, $P = .74$
TAOS	**0.33, $P = .01$**	**0.48, $P < .001$**	**0.59, .04**	**0.25, $P = .01$**	**0.63, $P < .001$**	0.79, $P = .08$

Correlations between baseline parameters and adiponectin were tested by Pearson rank correlation coefficient for data with a normal distribution. The r and P values are shown. Significant correlations are in bold. Within the sample, urinary albumin data were available on 323 subjects. Although we felt that sex stratification was important because of baseline difference in adiponectin between men and women, for men and women combined, the correlations between TAOS and adiponectin in the 3 groups were significant (normoalbuminuria: $r = 0.268$, $P < .001$; microalbuminuria: $r = 0.485$, $P < .001$; macroalbuminuria: $r = 0.62$, $P = .006$).

[a] Correlations between baseline parameters and adiponectin were tested by Spearman test for data that did not have a normal distribution (creatinine, duration of diabetes).

nephropathy in T1DM [29,34]. Within our current study of protected subjects, macroalbuminuria was associated with increased serum adiponectin in men, but not women. Within this study, we observed that serum adiponectin was higher in women compared with men. This is in line with previous observations [5,35]. The sex differences between men and women in serum adiponectin may be related to the production of different isoforms of adiponectin, which were not measured in this study. Of note, subjects with T1DM and women produce higher levels of the high–molecular mass isoform that is known to differ in its receptor binding properties and metabolic effects [36,37]. Furthermore, there may be sex-related differences in the genetic regulation of adiponectin expression [38]. In our study, it would be very difficult to disentangle the relationship between macroalbuminuria and kidney function, as both are clearly related in the pathophysiology of diabetic kidney disease and this is reflected by the increase in creatinine and reduced eGFR in men. There is a nonsignificant trend across the female groups in both of these measures (possible due to the smaller numbers in the women). However, when men and women were combined, the correlations between TAOS and adiponectin in the 3 groups were significant. Previous studies in adults with T1DM have shown a variable relationship between adiponectin levels and glycemic control with a negative [39], a positive [40], or no correlation at all [4]. We observed no relationship between glycemic control and adiponectin in this study, but HbA_{1c} was associated with urinary albumin excretion.

We observed that serum adiponectin had a positive correlation with plasma TAOS in both men and women. Therefore, an increase in adiponectin was associated with an increase in antioxidant status and reduced oxidative cellular burden. This is an interesting observation because progression from normoalbuminuria to macroalbuminuria and other microvascular complications relating to diabetes are related to increased oxidative stress and inflammatory mediated cell damage [2,41]. Low adiponectin levels are associated with insulin resistance [5], endothelial dysfunction [6], obesity [7], T2DM [8], CHD [9], and hypertension [10], all of which are related to increased inflammation and cellular oxidative damage. Furthermore, low levels of adiponectin are associated with increased oxidative stress [14]; and in vitro studies suggest that adiponectin may lower oxidative stress [15,16]. Previously, an inverse correlation has been observed between urinary levels of 8-epi-prostaglandin $F_{2\alpha}$, a marker of oxidative stress, and blood levels of adiponectin in humans [17,18]. Studies have also shown that the cardiac tissue from adiponectin knockout mice have higher levels of superoxide and peroxynitrite after myocardial ischemia compared with wild type [15]. After giving adiponectin before reperfusion, the knockout mice showed reduced myocardial ischemia–induced superoxide production and peroxynitrite formation, and reversed proapoptotic and infarct enlargement [15]. Similarly, in adult rats fed a high-fat diet, studies using isolated aortic segments demonstrate that adiponectin protects the endothelium against hyperlipidemic injury by multiple mechanisms, including promoting endothelial nitric oxide synthase activity, inhibiting inducible nitric oxide synthase activity, preserving bioactive nitric oxide, and attenuating oxidative/nitrative stress [16]. These effects may therefore be directly related to lower levels of adiponectin. In both sexes, the correlation between adiponectin and TAOS was most marked in those with micro-/macroalbuminuria. This correlation increased in a linear manner across the urinary albumin excretion groups so that, in the face of increased albumin excretion, an increase in adiponectin was closely related to an increase in antioxidant activity. Therefore, the paradoxical higher levels of adiponectin observed in the setting of nephropathy might represent a compensatory mechanism for increased inflammatory and oxidative cellular damage.

There are limitations to our study. We have chosen from the outset to examine one biochemical marker of oxidative stress. There may be some limitations to this measurement as discussed elsewhere [32,42-45]. These are mainly related to the specificity of plasma TAOS in relation to individual indices of antioxidant proteins or enzymes (eg, glutathione-s-transferase, vitamin C). However, we have found this to be a robust marker in many studies [32,42]. Further studies should incorporate additional plasma markers of oxidative stress within the analysis. At the time of analysis, assays were not available to measure the different isoforms of adiponectin; and furthermore, there were a limited number of samples available where adiponectin could be measured.

In summary, this study for the first time suggests a possible mechanism to explain the increase in adiponectin levels observed in subjects with T1DM and nephropathy. Further work is required to elucidate the mechanism by which the change in plasma adiponectin occurs. We also suggest an antioxidant role for adiponectin. Further prospective study is necessary to explore these observations. Such work might include adiponectin knockout animal models of diabetic nephropathy or the study of gene variants that may influence plasma levels of adiponectin in cohorts of subjects with T1DM and nephropathy.

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