Original Article

Study of Association of Serum Prolactin Levels with Insulin Resistance in Type 2 Diabetes Mellitus Patients

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Abstract

Objective: Prolactin (PRL) regulates glucose metabolism and insulin sensitivity. The study aimed to evaluate the role of PRL in glucose homeostasis and its association with insulin resistance in patients with diabetes mellitus (DM). **Methods and Materials:** This cross-sectional, observational study included 100 patients (25–60 years) with T2DM. Primary information including demographics, anthropometric measurements, and biochemical measures (complete blood count, glucose parameters, liver and kidney function test, lipid profile, thyroid function test, serum fasting insulin levels, serum PRL levels) was collected. **Results:** A total of 100 patients, 50 men and 50 women (25 premenopausal and 25 postmenopausal), were enrolled in this study. The correlation between serum cholesterol and PRL was found to be statistically non-significant ($P = 0.129$) in men and significant ($P = 0.041$) in women. There was an inverse relationship between fasting plasma glucose and serum PRL levels in both men ($r = -0.88$; $P < 0.0001$) and women patients ($r = -0.768$; $P < 0.0001$). Negative correlation between postprandial plasma glucose and PRL was found to be statistically significant ($r = -0.398$; $P = 0.048$) in postmenopausal women. The comparison in both men and women indicated an inverse correlation between serum PRL and glycated haemoglobin levels. There was a significant negative correlation between homeostasis model assessment-estimated insulin resistance (HOMA-IR) and PRL levels in both men ($r = -0.362$; $P = 0.039$) and women patients ($r = -0.362$; $P = 0.003$). Homeostasis model assessment of β cell function (HOMA-β), which directly correlates with residual pancreatic beta cell function, was positively correlated with prolactin levels, irrespective of gender and menopausal status of female subjects. **Conclusion:** Serum PRL levels correlate with improved glycaemic control.

Keywords: Glycaemic control, insulin resistance, prolactin

Introduction

Diabetes mellitus (DM) is a broad group of metabolic disorders that share the common phenotype of hyperglycaemia. Worldwide prevalence of diabetes has risen dramatically over the past three decades, from 108 million in 1980 to an estimated 422 million in 2014.[1] Diabetes mellitus and its associated complications owing to poor glycaemic control are a leading cause of hospitalization and ICU admission, morbidity, and mortality in diabetic individuals. DM is associated with decreased longevity; diabetic men live an average 7.5 years less while diabetic women live an average of 8.2 years less compared to healthy individuals.[2]

Prolactin (PRL), a polypeptide hormone, besides its lactogenic properties, has also been related to growth and development, immune regulation, and metabolism.[3,4] During second half of pregnancy, maternal PRL increases and stimulates β cell proliferation, insulin production, and secretion,[5,6] thus partly counteracting the diabetogenic effects of human chorionic somatomammotropin, cortisol, progesterone, and other hormones. Studies have demonstrated that effects of PRL though more pronounced in later half of pregnancy, are not entirely confined to pregnancy period.[4] During the nonpregnancy period also, prolactin plays a role in normal glucose homeostasis by stimulating β cells and insulin secretion and inhibiting key caspases of intrinsic and extrinsic pathways of islet apoptosis.[7,8]

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In experimental studies, prolactin has been shown to play an important role in regulating glucose metabolism and whole-body insulin sensitivity by increasing β cell proliferation,[9] promoting cumulative insulin secretion, and modulating immune function. It has an indirect action by increasing hypothalamic dopamine synthesis and improving energy and glucose homeostasis.[10] Interestingly, recent studies discovered that human adipose tissue produces PRL and also expresses PRL receptors,[11] highlighting a previously less thought of the action of PRL as a cytokine that might be involved in adipose tissue function. PRL has been shown to regulate adipose tissue function by downregulating lipoprotein lipase and fatty acid synthase,[11] which consequently suppresses lipogenesis. It has been shown to regulate the bioactivities of adipokines such as adiponectin, interleukin-6, and possibly, leptin also.[12]

The extra-mammary expression of prolactin receptors (PRLR), especially adipocytes and pancreatic islets, accounts for major metabolic and insulin-sensitizing effects in non-lactating women, including postmenopausal, and men. PRL-induced activation of insulin-receptor substrate phosphatidylinositol 3-kinase (IRS/PI 3-kinase) via JAK/STAT pathway[13] and inhibition of release of pro-inflammatory adiponectin and IL-6 have been demonstrated at physiological levels among women and men. In fact male prostatic tissue has also been found to express PRLR, augmenting citrate synthesis by prostatic cells.[14] Thus, the physiologic role of prolactin spans ages and genders.

Collectively, these studies raise the prospect that prolactin plays a definite role in energy homeostasis through its action as an adipokine and is involved in the manifestation of insulin resistance (IR). In our study, we evaluated the role of prolactin in glucose homeostasis and its association with insulin resistance in diabetic patients.

Methods

This was a cross-sectional, observational study carried out on 100 subjects aged 25–60 years (50 males, 50 females), visiting the Department of Medicine at a tertiary care hospital over a period of one year.

Individuals aged 25–60 years and diagnosed diabetics were involved. Subjects with conditions like pituitary prolactinoma, acromegaly, thyroid disorders, seizure disorder, history of head injury, oophorectomy and hysterectomy, abnormal liver function tests, abnormal kidney function tests, pregnant, and lactating females were excluded from the study.

As per the predesigned proforma, detailed history was taken. Subjects who were current smokers, had significant alcohol intake, or were on drugs specifically affecting prolactin and dopamine levels (namely, dopamine receptor blockers [antipsychotic medications, metoclopramide, domperidone], dopamine synthesis inhibitors including α-methyldopa, opiates, amitriptyline, selective serotonin reuptake inhibitors, antiseizure medications, etizolam, verapamil, oestrogens and hormone replacement therapy, exogenous steroids, antiretroviral therapy, statins) and exogenous insulin were excluded from the study.

Anthropometric measurements including weight (in kg), height (in m), waist circumference (in cm), hip circumference (in cm), and waist/hip ratio were measured. Complete blood counts, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), liver function tests, kidney function tests, glycated haemoglobin levels (HbA1c levels), serum fasting, and postprandial insulin levels and serum prolactin levels were measured.

All the issues including ethical issues of the protocol were evaluated by the Institutional Review Board and approved.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Ethical Clearance Statement

Institutional Review Board and Ethical Committee, Atal Bihari Vajpayee Institute of Medical Sciences (formerly Post Graduate Institute of Medical Research and Education) & Dr. RML Hospital, New Delhi. Approval number-01 - 45/21/2017/IC/THESIS/PGIMER-RMLH/10234.Approval date: 11/10/2017). Written and informed consent was obtained from the participants for participation in the study and use of patient data for research and educational purposes. Study protocol and procedures follows the guidelines laid down by Indian Council of Medical Research and Declaration of Helsinki (2013).

Results

A total of 100 subjects presenting to outpatient Department of Medicine were enrolled in the study. Fifty males and 50 females out of which 25 were premenopausal and 25 postmenopausal, were included.

Mean parameters in study subjects:

- Mean BMI of males, premenopausal females, and postmenopausal females were 27.99 ± 3.97, 27.31 ± 3.9, and 28.67 ± 4 kg/m^2, respectively. Mean WHR in males, premenopausal females, and postmenopausal females were 1 ± 0.06, 0.97 ± 0.05, and 0.99 ± 0.07, respectively.
- The values for FPG and PPPG were 186.34 ± 45.28 and 248 ± 58 mg/dL, respectively in females, and 180.98 ± 40.91 and 260.88 ± 73.92 mg/dL, respectively, in male subjects. Mean FPG and PPPG, respectively, were 188.36 ± 47.96 and 251.84 ± 47.53 mg/dL in premenopausal females and 184.32 ± 43.33 and 244.16 ± 67.66 mg/dL in postmenopausal females.
- Male subjects had a mean HbA1c of 9.29 ± 2.2%, while female subjects had HbA1c of 9.22 ± 1.72%. In female group, premenopausal females had a lower mean HbA1c (8.78 ± 1.36%) compared to postmenopausal females (9.65 ± 1.94%).

- Mean fasting insulin in males and females was 8.6 ± 5.98 and 8.17 ± 5.23 μIU/ml, respectively, while it was 7.42 ± 5.5 and 8.92 ± 4.93 μIU/ml, respectively, in premenopausal and postmenopausal groups.
- Mean HOMA-IR in males and females was 4.02 ± 3.38 and 3.96 ± 3.43, respectively, while in premenopausal and postmenopausal females was 3.92 ± 4.37 and 3.99 ± 2.23, respectively. Similarly, mean HOMA-β in males and females was 28.01 ± 19.88 and 24.92 ± 13.3%, respectively; and 21.28 ± 9.3 and 28.55 ± 15.71% for premenopausal and postmenopausal females, respectively.
- Mean PRL values did not show any statistically significant difference in the male versus female group (8.11 ± 4.7 versus 7.14 ± 4.83 ng/ml) and premenopausal versus postmenopausal group (7.62 ± 5.32 versus 6.65 ± 4.35 ng/ml).

Correlation between serum prolactin levels and various other correlates:

Study participants were divided into four groups (quartiles) of serum prolactin levels [Table 1]. Quartile 1 had the lowest values of serum prolactin (≤5.16 ng/ml in males and ≤3.92 ng/ml in females), while quartile 4 had the highest serum prolactin values (≥8.59 ng/ml in males and ≥7.80 ng/ml in females).

Anthropometric indices and serum PRL: Body mass index in various quartiles did not show any particular trend in males as well as females. No statistically significant inference could be derived from the correlation between the two parameters [Table 2]. Waist/hip ratio was comparable in all the four quartiles in males as well as females, with no statistically significant difference among the quartiles [Table 2].

Glycaemic parameters and serum PRL: In males, it was observed that subjects in quartile 1 had the highest FPG while quartile 4 males had the lowest FPG (280 mg/dL in quartile 1, and 146.58 mg/dL in quartile 4) [Table 3], signifying the inverse relationship between FPG and serum PRL, the *P* value for comparison was <0.0001, which was statistically highly significant. While comparing mean FPG among female subjects, it was observed that quartile 1 had the highest FPG while quartile 4 had the lowest FPG values (265.85 mg/dL in quartile 1, 147.08 mg/dL in quartile 4), an inverse relationship between FPG and serum PRL. Comparison among the PRL quartiles for mean FPG in females had a statically significant *P* value of <0.0001 [Table 3]. While comparing premenopausal and postmenopausal females, similar observation was found. In premenopausal females, *P* value was <0.0001 while in postmenopausal females, the value was <0.0001.

Comparison of PPPG among various quartiles did not reveal any consistent correlation. In fact, in male subjects it was observed that the 4th quartile patients had a mean PPPG of 307 mg/dL which was highest among all quartiles. 2nd quartile patients had the lowest mean PPPG of 228 mg/dL [Table 3]. PPPG in female subjects showed a trend of progressive decrease from quartile 1 to quartile 4. Mean PPPG in 1st, 2nd, 3rd, and 4th quartile was 275.3 mg/dL, 240.9 mg/dL, 239.69 mg/dL,

Table 1: Serum prolactin quartiles

Prolactin quartiles (in ng/ml)	Males	Number of males	Females	Number of females
Quartile 1	≤5.16	13	≤3.92	13
Quartile 2	5.17-7.20	12	3.93-6.20	12
Quartile 3	7.21-8.58	13	6.21-7.80	13
Quartile 4	≥8.59	12	≥7.80	12

Table 2: Mean anthropometric indices (BMI and WHR) in female and male subjects in various quartiles

Parameter	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*
BMI in females (in kg/m^2) Mean±SD	28.2±4.23	29.3±3.44	28.99±3.96	25.37±3.34	0.065
BMI in males (kg/m^2) Mean±SD	26.18±3.09	26.57±4.72	27.06±4.29	25.82±2.75	0.906
WHR in females Mean±SD	0.95±0.04	0.96±0.05	1.02±0.06	0.98±0.06	0.066
WHR in males Mean±SD	1±0.04	1±0.09	0.98±0.05	1.03±0.03	0.18

Table 3: Mean glycaemic parameters (FPG, PPPG, and HbA1c) in females and males in various quartiles

Parameter	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*
FPG (in mg/dL) in females Mean±SD	265.85±60.49	229.08±40.51	199.38±19.7	147.08±23.51	<0.0001
FPG in males (in mg/dL) Mean±SD	280±57.47	197.42±25.34	179±23.96	146.58±19.38	<0.0001
PPPG in females (in mg/dL) Mean±SD	275.31±78.07	240.92±44.51	239.69±39.43	234.5±58.68	0.397
PPPG in males (in mg/dL) Mean±SD	252.54±56.86	228.25±36.45	256.62±97.12	307.17±74.78	0.052
HbA1c (in %) in females Mean±SD	12.24±1.64	9.27±0.91	8.93±0.72	7.23±0.65	<0.0001
HbA1C (in %) in males Mean±SD (%)	12.45±1.43	9.59±1.15	8.86±0.75	7.09±0.56	<0.0001

and 234.5 mg/dL, respectively. The statistical significance of the correlation, however, was not found ($P = 0.397$) [Table 3]. *P* value for this comparison in premenopausal females was 0.92, respectively, while in postmenopausal females, it was 0.048, which was significant.

In the male group, mean HbA1c values in 1st, 2nd, 3rd, and 4th quartile were 12.45%, 9.59%, 8.86%, and 7.09%, respectively. The results indicated that subjects with lower PRL values had higher HbA1c, thus indicating poor glycaemic control. This comparison also was statistically highly significant ($P = <0.0001$) [Table 3]. While comparing among female subjects, quartile 1 had highest mean HbA1c of 12.24, while quartile 4 had the lowest mean HbA1c of 7.23 ($P = <0.0001$). The negative correlation between the two variables was significant in premenopausal and postmenopausal groups [Table 3]. The comparison in both males and females indicated that subjects with a lower serum prolactin had higher HbA1c value, while subjects with higher PRL had a lower HbA1c, indicating direct association of serum prolactin with glycaemic control.

Serum fasting insulin levels in both male and female subjects did not reveal any specific trend amongst the quartiles. It was, however, observed that 4th quartile in males had the maximum level of mean fasting insulin levels (7.93 µIU/mL), while in females, mean fasting insulin was highest in the 1st quartile (12.16 µIU/mL) and lowest in 2nd quartile (8.35 µIU/mL). Both the comparisons did not have any statistical significance ($P = 0.489$ for male group, $P = 0.071$ for female group) [Table 3]. Mean PP insulin in male subjects was observed to be highest in 4th quartile (31.59 µIU/mL) and lowest in 2nd quartile (11.57 µIU/mL). No peculiar trend was observed between PP insulin values and serum PRL [Table 3]. Similarly, in female group, no definite correlation could be derived between the two variables [Table 3].

HOMA indices and serum PRL: Insulin resistance was measured using homeostasis model assessment of insulin resistance (HOMA-IR). In males, the mean HOMA-IR was observed to be maximum in quartile 1 (4.83 ± 2.56). Insulin resistance was found to be progressively improving with increasing PRL values and it was minimum in the 4th quartile (2.64 ± 1.33). Analysis in this group indicated inverse correlation between serum PRL and HOMA-IR index, *P* value being 0.039 [Table 4]. In females, it was observed that with increase in serum PRL quartile, insulin resistance as measured by HOMA-IR decreased progressively. Mean HOMA-IR in 1st, 2nd, 3rd, and 4th quartile was 7.88 ± 2.98, 4.88 ± 3.09, 4.41 ± 2.36, and 3.41 ± 2.42, respectively. *P* value was 0.003 which was statistically significant [Table 4]. When compared separately between premenopausal and postmenopausal females, the comparison still held significance with a *P* value of 0.0131 in premenopausal and 0.0001 in postmenopausal females. Thus, irrespective of menopausal status, serum PRL correlated inversely with insulin resistance in females.

Beta cell function and insulin secretion were assessed using the HOMA-β index. It was observed that in male subjects, 1st quartile had the lowest mean HOMA-β (12 ± 5.15), while 4th quartile had the highest mean HOMA-β (34.51 ± 8.42). *P* value for this association was <0.0001, which is highly significant positive correlation [Table 4]. In females, no consistent relationship was observed between the various quartiles and HOMA-β values. However, quartile 4 had the highest mean HOMA-β value, i.e., maximum beta cell function [Table 4]. The association was significant in premenopausal and postmenopausal female subjects. *P* value for premenopausal females was 0.007 and 0.049 for postmenopausal females. The results, so obtained, indicated that higher prolactin levels correlate with a higher beta cell function represented by the HOMA-β index irrespective of gender and menopausal status of female subjects [Table 4].

Discussion

The pathophysiology of diabetes mellitus involves complex mechanisms. The role of prolactin apart from gestational state has been controversial, with limited studies in the nonpregnant population.

This study was a cross-sectional, observational study in which 100 diabetic patients were enrolled. Statistical association of serum PRL and insulin resistance and other indices of glycaemic control and anthropometric measures was studied.

Overall, the mean age of males and females was 46.42 ± 8.67 and 44. 8 ± 8.77 years, respectively. In study done by Chahar C *et al.*,[15] the mean age was 53.5 ± 5.4 years in diabetic males and 55.8 ± 5.1 years in female diabetic patients. The mean

Table 4: Mean insulin levels (fasting and postprandial) and HOMA indices in females and males in various quartiles

Parameter	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*
Fasting insulin in females (µIU/mL) ± SD	12.16±3.6	8.35±4.32	9.21±5.33	9.17±5.7	0.071
Fasting insulin in males (µIU/mL) Mean±SD	6.88±2.72	7.13±3.55	6.18±2.36	7.93±2.54	0.489
PP insulin in females (µIU/mL) Mean±SD	13.01±10.85	14.73±12.16	21.6±6.76	16.2±9.44	0.019
PP insulin in males (µIU/mL) Mean±SD	24.99±15.88	11.57±7.28	22.29±23.28	31.59±24.17	0.013
HOMA-β (in %) in females Mean±SD	24.57±2.64	18.7±9.23	25.67±16.63	41.91±27.72	0.03
HOMA-β (in %) in males Mean±SD	12±5.15	20.12±10.3	20.16±10.1	34.51±8.42	<0.0001
HOMA-IR in females Mean±SD	7.88±2.98	4.88±3.09	4.41±2.36	3.41±2.42	0.003
HOMA-IR males Mean±SD	4.83±2.56	3.43±1.77	2.71±0.97	2.64±1.33	0.039

age in our study did not correspond to this study by Chahar C *et al.*[15] because they did not include premenopausal females. However, we included premenopausal females as well because of the increasing incidence of obesity, insulin resistance, and shifting trend of diabetes towards the younger age group.

The mean BMI in our study was observed to be 27.99 ± 3.97, 27.31 ± 3.9, and 28.67 ± 4 kg/m^2 in males, premenopausal females, and postmenopausal females, respectively. This was in accordance with mean BMI observed by Chahar C *et al.*[15] in their study which had a mean BMI 25.99 ± 2.12 in males 26.01 ± 1.87 in postmenopausal females. We could not find any correlation between BMI and serum PRL in either males or females. However, Ernst B *et al.* (2009)[16] in 344 obese subjects found no correlation between basal PRL levels with the BMI of the subjects (r = −0.05, P = 0.77) even after adjusting for the impact of gender. Chirico *et al.*[17] described similar results of inverse correlation between BMI and serum PRL. Glintborg D *et al.*[18] also found that patients with lower PRL had higher mean BMI compared to controls (27.4 versus 25.0 kg/m^2). The difference might relate to variation in ethnicity and the study inclusion criteria.

Central obesity as determined by waist circumference and waist/hip ratio was assessed in males and females. Mean WHR was 1.03 ± 0.03 in males and 1.02 ± 0.06 in females. There was no statistically significant difference between the two groups in our study. However, Friedrich N *et al.*,[19] waist circumference and WHR, were inversely correlated to serum prolactin in women but not in men. Glintborg D *et al.*[18] also found an inverse correlation between serum PRL and waist circumference (90.0 cm versus 80.0 cm in cases versus controls). These studies were done in non-diabetic subjects and did not exclude pathological hyperprolactinemia. Results may not be applicable to the Asian population due to increased genetic susceptibility for central adiposity.

Glycaemic traits were assessed using FPG, PPBS, HbA1c, serum insulin levels, and HOMA indices. Our study found a statistically significant correlation between serum PRL and fasting plasma glucose. It was observed that the highest FPG in 1st quartile of PRL and lowest in the 4th quartile of PRL in both males and females, meaning thereby, that serum PRL concentration inversely correlates with FPG values, irrespective of gender. Wagner R *et al.*[20] also described similar results in their study. They found that AUC_{0-120} glucose correlated negatively with prolactin. Similar results were demonstrated by Chahar C *et al.*[15] However, no correlation could be inferred from the results between PPBS and serum PRL.

Derivation of correlation between PRL and HbA1c indicated that subjects with lower PRL values had higher HbA1c, thus indicating poor glycaemic control. In the male group, mean HbA1c values in 1st and 4th quartile were 12.45% and 7. 09%, respectively, while in females, quartile 1 had the highest mean HbA1c of 12.24, while quartile 4 had the lowest mean HbA1c of 7.23 (P = <0.001). Furthermore, this was in concordance with study by Wanger R *et al.*[20] which showed a similar association between prolactin and HbA1c after adjustment for age, gender, and BMI (P < 0.0001). Study by Chahar C *et al.*[15] also had similar results with mean HbA1C 7.0%, 6.4% 6.1%, and 5.9% in males, and 7.2%, 6.7%, 6.3%, and 5.8% in females in 1st, 2nd, 3rd, and 4th quartile, respectively. Thus, it was evident that prolactin has significant impact on glycaemic control, with an evident negative correlation (P < 0.001) between PRL and HbA1c values.

HOMA-IR and HOMA-β were used to determine insulin resistance and pancreatic beta cell function. The analysis revealed that insulin resistance progressively improved with increasing PRL values. In males, the mean HOMA-IR was observed to be maximum in quartile 1 (4.83 ± 2.56), and it was minimum in 4th quartile (2.94 ± 1.33). In females also, HOMA-IR was found to be progressively decreasing with increasing levels of serum PRL, a statistically significant correlation. Our results were in harmony with those obtained by a study by Chirico V *et al.*[17] who studied serum prolactin in obese children and prospectively found that a decrease of PRL was associated with a 10% increased risk of progression to overt diabetes mellitus. Daimon M *et al.*[21] also found that serum PRL levels significantly correlated with HOMA-IR, even after adjustments for multiple factors correlated with HOMA-IR in univariate correlation analyses (P = 0.035).

In our study, males in 1st quartile had the lowest mean HOMA-β (12 ± 5.15), while 4th quartile had the highest mean HOMA-β (34.51 ± 8.42); P value being <0.001. Comparison in female group also revealed that minimum value of HOMA-β was in quartile 1, while maximum value was observed in quartile 4. Mean HOMA-β was highest in quartile 4, followed by quartile 3, and lowest in quartile 2. P value for this correlation was 0.03. Daimon *et al.*,[21] however, could not establish such correlation with HOMA-β.

Although the research was carefully prepared and has reached its aim, there were some unavoidable limitations. First, the research was conducted on small sample size and from a single institute. Large-scale studies involving various populations and ethnic groups are needed to unveil consistent associations. Second, the causal relationship between prolactin and insulin resistance and diabetes could not be conclusively established as it was a cross-sectional study. Follow-up longitudinal studies are required to establish a causal relationship.

Conclusion

Globally, diabetes mellitus has reached epidemic dimensions. Despite upcoming newer treatment modalities, poor glycaemic control causes immense morbidity and mortality as well. Factors determining insulin resistance remain elusive. Prolactin has been studied extensively in the pregnant state and gestational diabetes; however, its role in non-gestational state remains controversial. While pathological hyperprolactinemia promotes a state of insulin resistance, higher prolactin values within the physiological range improve insulin

sensitivity and correlate with improved glycaemic control. In our study, we found that higher serum prolactin levels correlate with improved glycaemic control, irrespective of gender and irrespective of the menopausal status of female subjects. Also, insulin secretion by pancreatic beta cells and improved insulin resistance corelate positively with prolactin levels. The study suggests an important role of prolactin in pathophysiology of insulin resistance and diabetes mellitus. However, clinical importance of such observations and therapeutic considerations still need to be explored. Drugs affecting prolactin concentration can play an important role in the management of insulin resistance and diabetes, though a long way ahead.

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Conflicts of interest

There are no conflicts of interest.

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