Hypoadiponectinaemia enhances waist circumference as a predictor of glucose intolerance and clustering of risk factors in Chinese men

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Abstract

Aim. – This study aimed to confirm the hypothesis that adiponectin levels can enhance the discriminative value of waist circumference (WC) in predicting impaired glycaemic status and clustering of risk factors.

Methods. – We used receiver operating characteristic (ROC) curve analysis to define the optimal cut-off value of adiponectin to predict diabetes in Chinese men with no relevant past medical history. This value was combined with WC to increase its discriminative power in ascertaining impaired glycaemic status and various cardiovascular risk factors.

Results. – In 360 men (mean ± S.D.; age: 41.3 ± 9.2 years), the mean ± S.D. adiponectin level was 5.2 ± 2.7 μg/mL. Based on oral glucose tolerance tests (OGTTs), 84 men (23.3%) had undiagnosed diabetes, 52 (14.4%) had impaired glucose tolerance (IGT) and 224 (62.3%) had normal glucose tolerance. On ROC analysis, 5.7 μg/mL was the optimal cut-off value of adiponectin in this population to predict diabetes. Compared with subjects who had normal WC (defined as less than 90 cm) and high adiponectin levels (≥ 5.7 μg/mL), the likelihood ratio of diabetes was 2.54 in those with central obesity and hypoadiponectinaemia.

Conclusion. – The combined use of low adiponectin levels and large WC measures has greater discriminative power than using either index alone to identify subjects at particular risk of glucose intolerance and clustering of risk factors.

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Keywords: Adiponectin; Obesity; Diabetes; Insulin resistance

Résumé

La détermination des concentrations plasmatiques d’adiponectine améliore la valeur discriminative du tour de taille pour prédire les anomalies de la tolérance au glucose et les facteurs de risque cardiovasculaires chez des chinois de sexe masculin.

Objectif. – Démontrer l’hypothèse que la détermination des concentrations plasmatiques d’adiponectine améliore la valeur discriminative du tour de taille pour prédire les anomalies de la tolérance au glucose et les facteurs de risque.

Méthodes. – Nous avons utilisé l’analyse ROC pour définir la valeur seuil d’adiponectine de prédire le diabète chez des chinois de sexe masculin, indemnes d’antécédents médicaux. Cette valeur a été combinée avec le tour de taille pour accroître son pouvoir discriminant pour prédire les anomalies de la tolérance au glucose et les facteurs de risque cardiovasculaire.

Résultats. – Dans cette population qui comportait 360 hommes âgés de 41,3 ± 9,2 ans, les concentrations plasmatiques moyennes d’adiponectine (± S.D.) étaient de 5,2 ± 2,7 μg/mL. Une Oral Glucose Tolerance Test (OGTT) a permis de classer les sujets en diabète méconnu (n = 84, 23,3 %), intolérance au glucose (n = 52, 14,4 %) et tolérance au glucose normale (n = 224, 62,3 %). L’analyse ROC a montré qu’une concentration plasmatique d’adiponectine de 5,7 μg/ml était la valeur seuil optimale pour prédire le diabète. Par rapport aux sujets qui présentaient un tour de taille normal (< 90 cm) et des concentrations plasmatiques d’adiponectine élevées (≥ 5,7 μg/mL), le risque de développer un diabète était de 2,54 chez les sujets qui présentaient une obésité centrale et une hypoadiponectinémie.

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1. Introduction

Adiponectin, which is secreted exclusively by adipocytes [1], possesses anti-inflammatory, insulin-sensitizing, antiatherogenic and antiangiogenic functions [2–4]. Many studies have confirmed the association of low adiponectin levels with obesity and, especially, with central obesity [5,6], insulin resistance (IR) and atherosclerosis [1,7,8]. Waist circumference (WC) has been proposed as a screening test for visceral obesity and for the identification of subjects at high-risk of developing diabetes and atherosclerosis. However, the optimal cut-off value of WC to define central obesity remains a matter of debate, especially in non-Caucasian populations [9].

Several prospective studies that included Chinese populations have confirmed the independent value of adiponectin in predicting hypertension, new-onset diabetes, the metabolic syndrome and cardiovascular events [10–13]. We hypothesized that the combined use of measures of adiponectin and WC might increase their discriminative power in identifying high-risk subjects for clusters of risk factors. To test this hypothesis, we examined 360 middle-aged Chinese men with no known relevant medical history. All of these men had participated in a community-based health-screening survey for glucose intolerance.

2. Methods

2.1. Participants and study design

The present study participants were a subset recruited from the Better Health for Better Hong Kong (BHBHK) programme, a health-promotion survey conducted between 2000 and 2002 and involving nearly 10,000 subjects [14]. The 360 men were randomly selected to undergo detailed clinical assessment at the Prince of Wales Hospital in Hong Kong [15]. The study was approved by the clinical research ethics committee of the Chinese University of Hong Kong and complied with the Declaration of Helsinki, with written informed consent obtained from all participants for data analysis and reporting.

All subjects attended the hospital centre after at least 8 h of an overnight fast to undergo anthropometric measurements and laboratory investigations. Body mass index (BMI) was calculated as weight in kilogrammes (kg), divided by the square of height in metres (m). WC was taken as the smallest circumference between the umbilicus and xiphoid process and measured to the nearest 0.5 cm. Also, after sitting for at least 5 min, blood pressure (BP) was measured in the right arm using a Dinamap machine (Critikon Inc., Tampa, FL, USA). The mean value of two readings, taken 1 min apart, was used in the analyses. General obesity was defined as a BMI greater or equal to 27.5 kg/m² [16], while central obesity was defined as a WC greater or equal to 90 cm [17].

2.2. Laboratory assays

All subjects underwent a 75-g oral glucose tolerance test (OGTT), with measurement of fasting and 2-h plasma glucose (PG). Fasting blood was also taken for measurement of lipid profiles [total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)] and adiponectin, using the Roche DP Modular Analytics system (Roche Molecular Biochemicals, Mannheim, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald’s formula [18]. Both intra-assay and interassay (CV) for PG were 2% at 6.6 mmol/L. Interassay CV for lipids were: TC, 1.9% at 6.4 mmol/L; TG, 2.6% at 1.9 mmol/L; and HDL-C, 5.4% at 0.86 mmol/L. Adiponectin assay was performed using Quantikine Immunoassay (R&D Systems, Minneapolis, MN, USA). The between-batch CV was less than 10% for different adiponectin concentrations. Hypoadiponectinaemia was defined as adiponectin levels lower than the optimal value for predicting diabetes, using the receiver operating characteristic (ROC) curve method.

2.3. Statistical analysis

Statistical analyses were performed using SPSS (version 15.0) software on an IBM-compatible computer. All results are expressed as means ± S.D., number (%) and geometric mean x/± antilog S.D., with 95% confidence intervals (CI) where appropriate. TG levels were logarithmically transformed for statistical tests in cases of skewed distributions. World Health Organization (WHO) criteria were adopted to define diabetes (fasting PG ≥ 7 mmol/L and/or 2-h PG ≥ 11.1 mmol/L), impaired glucose tolerance (impaired glucose tolerance [IGT]; fasting PG < 7 mmol/L and 2-h PG 7.8–11.1 mmol/L) and normal glucose tolerance (NGT; fasting PG < 7 mmol/L and 2-h PG < 7.8 mmol/L).

Student’s t test and the Chi² test were used for between-group comparisons where appropriate and analysis of covariance (ANCOVA) was also used, with age, smoking, BMI and WC as covariates. ROC curve analysis was performed to estimate the optimal level of variables in predicting diabetes. The area under the ROC curve (AUC) was estimated for test accuracy (the sum of sensitivity and specificity). Binary logistic regression was used to assess the prediction of diabetes with age, WC, BP,
Table 1
Clinical characteristics of the 360 Chinese male study participants by glycaemic status.

|                      | Overall (n = 360) | Normal (n = 224) | IGT (n = 52) | Diabetes (n = 84) | P value | Adjusted P value*
|----------------------|------------------|------------------|-------------|-----------------|---------|-----------------
| Age (years)          | 41.3 ± 9.2       | 40.3 ± 9.0       | 42.4 ± 9.4  | 43.4 ± 9.4      | 0.020   | –                
| Smoking              | 108 (30.1)       | 56 (25.0)        | 19 (36.5)   | 33 (39.3)       | 0.028   | –                
| BMI (kg/m²)          | 25.3 ± 3.8       | 24.7 ± 3.4       | 26.6 ± 4.4  | 27.0 ± 3.8      | <0.001  | –                
| WC (cm)              | 86.6 ± 9.7       | 84.2 ± 8.5       | 89.1 ± 11.0 | 91.4 ± 10.0     | <0.001  | –                
| Systolic BP (mmHg)   | 125 ± 17         | 122 ± 16         | 127 ± 20    | 130 ± 18        | <0.001  | 0.291            
| Diastolic BP (mmHg)  | 79 ± 11          | 77 ± 11          | 82 ± 13     | 80 ± 11         | 0.009   | 0.425            
| TC (mg/dL)           | 5.41 ± 1.01      | 5.37 ± 1.03      | 5.47 ± 0.91 | 5.45 ± 1.01     | 0.735   | 0.797            
| TG (mmol/L)b         | 1.48 × 1.82      | 1.32 × 1.72      | 1.75 × 1.92 | 1.84 × 1.89     | <0.001  | 0.037            
| HDL-C (mmol/L)       | 1.27 ± 0.32      | 1.33 ± 0.32      | 1.27 ± 0.31 | 1.13 ± 0.28     | <0.001  | 0.008            
| LDL-C (mmol/L)       | 3.36 ± 0.87      | 3.36 ± 0.90      | 3.33 ± 0.81 | 3.37 ± 0.81     | 0.962   | 0.378            
| 0-h PG (mmol/L)      | 5.88 ± 2.03      | 5.05 ± 0.54      | 5.34 ± 0.44 | 8.57 ± 2.68     | <0.001  | <0.001           
| 2-h PG (mmol/L)      | 7.14 ± 3.40      | 5.46 ± 1.30      | 9.03 ± 0.87 | 13.78 ± 3.14    | <0.001  | <0.001           
| Adiponectin (µg/mL)  | 5.19 ± 2.69      | 5.72 ± 2.94      | 4.60 ± 2.10 | 4.16 ± 1.81     | <0.001  | 0.001            
| General obesity      | 92 (25.6)        | 44 (19.6)        | 17 (32.7)   | 31 (36.9)       | 0.004   | 0.640            
| Central obesity      | 126 (35.0)       | 57 (25.4)        | 24 (46.2)   | 45 (53.6)       | <0.001  | 0.688            

Data are expressed as means ± S.D. or n (%).
IGT: impaired glucose tolerance; BMI: body mass index; WC: waist circumference; BP: blood pressure; TC: total cholesterol; TG: triglyceride; HDL-/LDL-C: high-/low-density lipoprotein cholesterol; 0-h/2-h PG: fasting/2-h plasma glucose.
General obesity: BMI ≥ 27.5 kg/m²; central obesity: waist ≥ 90 cm.

* Adjusted for age, smoking, BMI and waist circumference.

** Geometric mean × antilog S.D.

TG, HDL-C and adiponectin as independent parameters. Linear-regression analyses, with accumulated rates of having diabetes, IGT or obesity as independent variables, were performed to predict their associations with every 1-µg/mL reduction in adiponectin level. The likelihood ratio (LR) was calculated using the following equation: LR = sensitivity/(1 - specificity) [19]. A P < 0.05 (two-tailed) was considered to be significant.

3. Results

The mean (± S.D.) age of the present study’s 360 men was 41.3 ± 9.2 years (median: 41.0 years; range: 16–72 years). In this cohort, the mean adiponectin level was 5.2 ± 2.7 µg/mL and 39.4% (n = 142) had hypoadiponectinaemia. Also, 84 (23.3%) men had diabetes, 52 (14.4%) had IGT and 224 (62.3%) had normal glucose tolerance (NGT). Their clinical characteristics, categorized according to glycaemic status, are shown in Table 1. With deteriorating glycaemia from NGT to IGT to diabetes, HDL-C and adiponectin levels progressively decreased while fasting TG progressively increased. Using BMI to define general obesity, obese diabetic men had the lowest adiponectin levels at 3.79 ± 1.42 µg/mL, while non-obese men with NGT had the highest levels at 5.87 ± 2.93 µg/mL (P < 0.001). Similarly, subjects with central obesity and diabetes had the lowest adiponectin values compared with those who had normal WC and NGT and the highest levels of adiponectin (3.84 ± 1.45 vs 6.26 ± 2.94 µg/mL, respectively; P < 0.001).

With subjects categorized by adiponectin quartiles and after adjusting for age, smoking, BMI and WC, higher adiponectin values were associated with lower TG and 2-h PG, lower rates of diabetes and higher levels of HDL-C (data not shown). On ROC analysis, the optimal adiponectin level predictive of diabetes was 5.7 µg/mL, with an AUC of 0.642 (95% CI: 0.580–0.704; Fig. 1), which was therefore adopted as the cut-off point to define hypoadiponectinaemia in the present male Chinese cohort compared with the usual definition of hypoadiponectinaemia (<4 µg/mL) [7,20].

![Fig. 1](image-url)

Fig. 1. The receiver operating characteristic (ROC) curve analysis to predict diabetes, using waist circumference, adiponectin and a combination of both variables in the equation. Straight diagonal line: line of absence of discrimination; x axis: false-positive rate (1 − specificity); y axis: true-positive rate (sensitivity). In ROC plots, the closer the plot is to the upper-left corner, the greater is the accuracy (sum of sensitivity and specificity) of the test.
Table 2
Sensitivity and specificity of various factors in predicting diabetes.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Optimal cut-off valuea</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal waist circumference (cm)</td>
<td>87.8</td>
<td>72.3</td>
<td>62.0</td>
<td>1.90</td>
</tr>
<tr>
<td>Central obesity (cm)</td>
<td>90.0</td>
<td>53.6</td>
<td>70.7</td>
<td>1.83</td>
</tr>
<tr>
<td>Optimal BMI (kg/m²)</td>
<td>24.8</td>
<td>73.8</td>
<td>54.7</td>
<td>1.63</td>
</tr>
<tr>
<td>General obesity (kg/m²)</td>
<td>27.5</td>
<td>36.9</td>
<td>77.9</td>
<td>1.67</td>
</tr>
<tr>
<td>Optimal TG (mmol/L)</td>
<td>1.66</td>
<td>58.3</td>
<td>64.0</td>
<td>1.62</td>
</tr>
<tr>
<td>Optimal HDL-C (mmol/L)</td>
<td>1.23</td>
<td>76.2</td>
<td>56.0</td>
<td>1.73</td>
</tr>
<tr>
<td>Optimal systolic BP (mmHg)</td>
<td>125</td>
<td>67.2</td>
<td>62.5</td>
<td>1.79</td>
</tr>
<tr>
<td>Optimal diastolic BP (mmHg)</td>
<td>83</td>
<td>41.8</td>
<td>72.0</td>
<td>1.49</td>
</tr>
<tr>
<td>Hypoadiponectinaemia (µg/mL)</td>
<td>5.7</td>
<td>85.7</td>
<td>39.5</td>
<td>1.42</td>
</tr>
<tr>
<td>Hypoadiponectinaemia + central obesity</td>
<td>–</td>
<td>48.8</td>
<td>80.8</td>
<td>2.54</td>
</tr>
<tr>
<td>Optimal BMI + central obesity</td>
<td>–</td>
<td>52.4</td>
<td>72.1</td>
<td>1.88</td>
</tr>
<tr>
<td>Optimal TG + central obesity</td>
<td>–</td>
<td>34.5</td>
<td>82.6</td>
<td>1.98</td>
</tr>
<tr>
<td>Optimal HDL-C + central obesity</td>
<td>–</td>
<td>47.6</td>
<td>80.8</td>
<td>2.48</td>
</tr>
<tr>
<td>Optimal systolic BP + central obesity</td>
<td>–</td>
<td>32.1</td>
<td>85.1</td>
<td>2.15</td>
</tr>
<tr>
<td>Optimal diastolic BP + central obesity</td>
<td>–</td>
<td>21.4</td>
<td>86.2</td>
<td>1.55</td>
</tr>
</tbody>
</table>

LR: likelihood ratio; BMI: body mass index; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; BP: blood pressure.

Hypoadiponectinaemia: adiponectin < 5.7 µg/mL.
General obesity: BMI ≥ 27.5 kg/m²; central obesity: waist ≥ 90 cm.

As a predictor of the presence of diabetes, central obesity had a sensitivity and specificity of 53.6% and 70.7%, respectively and an LR of 1.83, while the corresponding figures for hypoadiponectinaemia (< 5.7 µg/mL) were 85.7%, 39.5% and 1.42. Combining central obesity and hypoadiponectinaemia raised the LR to 2.54 and specificity to 80.8% but sensitivity remained low at 48.8%. The sensitivity, specificity and optimal values for predicting diabetes of the other parameters based on ROC analysis are summarized in Table 2.

Using binary logistic regression analysis to predict diabetes, with age, WC, systolic and diastolic BP, TG, HDL-C and adiponectin levels as independent variables, only WC and adiponectin levels were statistically significant.

Fig. 1 shows the ROC curves with WC, adiponectin and both variables combined in the equation to predict diabetes. The AUC (95% CI) for adiponectin was 0.639 (0.576–0.702) and, for WC, 0.690 (0.626–0.754), which increased to 0.718 (0.656–0.779) when adiponectin was added to the prediction equation. On linear-regression analysis, for every 1-µg/mL reduction in adiponectin level, there were increases in the percentages of subjects with diabetes, IGT and general and central obesity, by 2.31%, 1.45% and 2.54% and 2.09%, respectively (although this may not be the case when adiponectin levels are beyond the usual range; see the discussion below). Fig. 2 shows the relationships between adiponectin levels and the corresponding cumulative rates of men with diabetes, IGT and obesity. When adiponectin was more than 9 µg/mL, the cumulative rates of those with IGT and diabetes were 1.1% and 0.6%, respectively, while those with general and central obesity were 1.1% and 1.9%, respectively.

At different WCs, the rates of glucose intolerance varied. As WC decreased, the rate of glucose intolerance also tended to decrease. Fig. 3 shows the relationship between increasing WC and the cumulative rates of diabetes and IGT. When WC was less or equal to 80 cm, the cumulative rate of men with either diabetes or IGT was 2.0–3.5%.

4. Discussion

Both obesity and diabetes are now worldwide pandemics [21,22] and the rapidly growing prevalence of obesity due to unhealthy lifestyles is a major factor [21]. In the present analysis, we found a progressive decline in adiponectin levels from NGT to IGT to diabetes. Although there are reports of an association between low adiponectin and the risk of diabetes in many populations, including Asian ones [23,24], its clinical usefulness remains debatable. By ROC curve analysis, we found that the optimal adiponectin value for predicting diabetes was 5.7 µg/mL, rather than the 4 µg/mL used in the conventional definition of hypoadiponectinaemia mostly reported in...
Caucasian populations [7,20]. To accommodate such interethnic differences found in risk associations, adopting a higher cut-off value to define hypoadiponectinaemia in the Chinese population should be considered.

Our subjects with diabetes and obesity (BMI ≥ 27.5 kg/m² or WC ≥ 90 cm) had a mean adiponectin level of 3.8 μg/mL—which was far lower than 5.7 μg/mL, the optimal level determined in the present study—thereby confirming the association between diabetes, obesity and hypoadiponectinaemia. For every 1-μg/mL reduction in adiponectin, the rates of men with IGT and diabetes increased by 1.5% and 2.3%, respectively. However, these figures need to be interpreted with caution, as a linear relationship was assumed in the regression analyses and such an assumption may only fit when adiponectin levels are within the usual range of 2–7 μg/mL, as in our study population (Fig. 2). Nevertheless, diabetes was unlikely in those who had high adiponectin levels, with less than 2% of those with adiponectin levels more than 9 μg/mL being glucose-intolerant.

Central obesity is now considered the main culprit behind IR and type 2 diabetes [25]. In recognition of its importance, central obesity is considered a prerequisite condition for the metabolic syndrome, according to the International Diabetes Federation (IDF) [17]. In the present study cohort, the WC cut-off value of more than 90 cm had a sensitivity of 54% and specificity of 71% (LR = 1.83) in predicting diabetes. In addition, other parameters that might increase the LR for predicting diabetes include BP, TG and HDL-C. In particular, HDL-C increased the LR from 1.83 to 2.48, which was similar to combining hypoadiponectinaemia with WC, which gave an LR of 2.54. This suggests that HDL-C is another important parameter to consider when assessing diabetes risk. However, given the potentially huge number of correlations, we did not analyze all the various combinations with these parameters. Nevertheless, our preliminary results suggest that, in addition to WC, other risk factors indicated for diabetes evaluation are adiponectin levels, HDL-C and systolic BP.

Indeed, the inclusion of adiponectin increased specificity up to 80.8%, although there was a trade-off with a reduced sensitivity of 48.8%. Compared with subjects who had small WCs and high adiponectin values, the LR for large WCs and low adiponectin in predicting diabetes increased to 2.5. According to the ROC curves, the AUCs for adiponectin and WC on their own were 0.639 and 0.690, respectively, which increased to 0.718 when both parameters were used in the prediction equation. The difference, however, is not large, suggesting a close association between WC and adiponectin.

However, the mechanism underlying the association between low adiponectin and diabetes is still not completely understood. Adiponectin has been reported to have a negative correlation with IR [7,8,26], although recent reports also suggest that it may have an effect on insulin secretion. In purified rat islets incubated with adiponectin (100 ng/mL) at low (3.3 mM) and high (16.7 mM) glucose concentrations, Gu et al. [27] found that insulin secretion was significantly increased in the presence of adiponectin at high glucose concentrations; however, these findings require independent replication.

The present study has several limitations: first, only men were included; and second, adiponectin was measured in its total circulating form. Nowadays, commercial kits to determine the high-molecular-weight (HMW) form of adiponectin are available. Compared with total adiponectin, HMW adiponectin may prove to be a better parameter for predicting diabetes. In addition, the “optimal” cut-off value for hypoadiponectinaemia derived from the present study subjects may not be applicable to other ethnic groups or to glucose abnormalities in other pathological conditions. More studies in this area are indicated.

In conclusion, the present study found a close relationship between obesity, adiponectin and diabetes—at least in Chinese men. There was also a progressive decline in adiponectin levels as glycaemic status deteriorated from NGT to IGT to diabetes. Finally, the use of both hypoadiponectinaemia and WC may overcome some of the inconsistent diabetes risk associations seen with WC used on its own as a screening test.

Conflict of interest
None.

References


