Adiponectin, leptin, interleukin-6 and HbA1c in the prediction of incident type 2 diabetes: A nested case–control study in Asian Indian men with impaired glucose tolerance

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Abstract

Aims: The aims of this study were: (1) to assess the association of adiponectin, leptin and interleukin-6 (IL-6) with incidence of type 2 diabetes (T2DM) in Asian Indian men with impaired glucose tolerance (IGT) and (2) to evaluate the additional contribution of these with the well-established glycaemic marker HbA1c.

Methods: This is an ancillary analyses of a nested case–control study derived from a prospective, prevention trial in India. All the participants had IGT at baseline. For this subanalysis a total of 147 (T2DM: 71; non-diabetic: 76) participants were selected based on the final glycaemic outcomes. Association of these selected adipokines with T2DM were assessed using logistic regression analyses. Clinical usefulness of adding adipokine markers with HbA1c on prediction of T2DM was assessed using the area under the curve (AUC) of the receiver operating characteristics.

Results: Baseline levels of adiponectin were lower and the levels of IL-6 were higher in T2DM cases when compared with non-diabetic cases (P < 0.05). Levels of leptin were similar in both groups. In fully adjusted models, adiponectin (odds ratio (OR): 0.55 [95%CI: 0.33–0.91]; P = 0.019) and IL-6 (OR: 2.27 [95%CI: 1.40–3.691]; P = 0.001) were associated with diabetes. Addition of adiponectin to HbA1c improved the AUC (ΔAUC: 0.0619; P = 0.0251), whereas addition of IL-6 did not improve the predictive power of HbA1c alone.

Keywords:
Adiponectin
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Abbreviations: AUC, area under curve; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; CPS, coefficients of variations; ELISA, enzyme-linked immunosorbent assay; EPIC, European prospective investigation into cancer and nutrition; HDL-chol, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IDPP-1, Indian diabetes primary prevention-1; IGT, impaired glucose tolerance; IGI, insulinogenic index; IL-6, interleukin (IL)-6; IQR, inter quartile range; NGT, normoglycaemia; OGTT, oral glucose tolerance test; OR, odds ratio; PAI-1, plasminogen activation inhibitor; RBP4, retinol binding protein-4; ROC, receiver-operating-characteristic; T2DM, type 2 diabetes mellitus; TNF-α, tumour necrosis factor-α; WHO, World Health Organisation.

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1. Introduction

Determining the optimal method for early identification of individuals at high risk for progression to diabetes remains challenging and is an area of considerable research interest. By the time dysglycemia occurs individuals are already near maximally insulin resistant and have lost almost 80% of the β-cell function [1]. Hence, the use of plasma glucose or Hba1c criteria defining specific thresholds for diagnosing dysglycemic states may be counterproductive and may ironically limit earlier detection of subtle dysglycemia and subsequent intervention. Therefore, it is imperative to identify alternate markers unrelated to glucose metabolism to identify high risk individuals.

The prevalence of dysglycemia is particularly high in Asian Indians who have several characteristic risk factors such as high prevalence of insulin resistance, high levels of body fat percentage and abdominal obesity [2]. Underlying these associations may be the secretion by adipocytes and macrophages that have migrated to adipose tissue, of biologically active mediators (adipocytokines), such as adiponectin, resistin, retinol binding protein-4 (RBP-4), tumour necrosis factor (TNF-α), interleukin-6 (IL-6), plasminogen activation inhibitor-1 (PAI-1), angiotensinogen, leptin and ghrelin [3–6].

Adiponectin differs from other adipokines in that it is inversely associated with obesity. Apart from its anti-inflammatory and insulin sensitising properties it is also involved in lipid clearance [6]. Recent meta-analysis of 13 prospective studies demonstrated that pooled relative risk of type 2 diabetes (T2DM) was 0.72 (95%CI, 0.67–0.78, P < 0.001) per 1 – log µg/ml increment in adiponectin levels [7].

Leptin is a regulator of satiety and body weight. It is positively associated with obesity, fat mass, insulin resistance, triglyceride level and inflammatory cytokines and negatively associated with HDL cholesterol [6]. Though a predictive association of leptin with T2DM has been demonstrated in white populations [8,9] its effect was attenuated when insulin resistance and other confounding variables were taken into account [9].

IL-6 is a major pro-inflammatory cytokine that acts on the liver to stimulate the production of a number of acute-phase proteins. Several cross sectional and prospective studies have shown a positive relationship between plasma IL-6 levels and dysglycemia [8,10–12].

Despite well-characterised protective effects of adiponectin (anti-inflammatory and insulin sensitising) and deleterious effects of IL-6 and leptin (pro-inflammatory and insulin resistance-inducing), the association of these adipokines with T2DM has not been explored in depth in Asian Indians.

Therefore the objectives of this study were: (1) to assess the association of adiponectin, IL-6 and, leptin with incident T2DM in Asian Indian men with IGT and (2) to evaluate the additional contribution of these biomarkers when combined with the well established glycaemic marker, HbA1c.

2. Methods and materials

2.1. Study design

This is an ancillary analysis of a nested case–control study. Participants were selected from a 2 year randomised, controlled prospective diabetes prevention programme carried out in India (ClinicalTrial.Gov no: NCT00819455). The study design, eligibility criteria, recruitment of participants, methods used and results have been described in the primary report [13]. The study protocol was approved by the Ethical Review Committee of the India Diabetes Research Foundation, Chennai, India. The study participants gave written informed consent prior to enrolment in the study. The study was conducted in Asian Indian men of working age group. In the original study, participants were randomly assigned either to the control group (n = 266) who received standard advice on healthy diet and physical activity at baseline or to the intervention group (n = 271) who in addition to the baseline lifestyle advice also received frequent motivational text messages on principles of healthy lifestyle through mobile phones. The participants were followed-up at intervals of 6-months for two years to assess their glycaemic status. The primary outcome was development of diabetes as classified by the World Health Organisation (WHO) criteria; a fasting plasma glucose of 7.0 mmol/l or higher and/or 11.1 mmol/l or higher 2 h after a 75-g oral glucose load [14]. The study showed that mobile phone based text messaging is an effective methodology in prevention of diabetes with a relative risk reduction of 36% [95%CI: 9–55].

At the end of the study, among the 517 responders (96.3%), 170 (32.9%) had reverted to normoglycaemia (NGT), 224 (43.3%) continued to have IGT and 123 (23.8%) had developed diabetes [13].

For this analysis, 71 participants who developed T2DM, and 76 age and BMI matched non-diabetic controls (NGT: 43; IGT: 33) were selected for the biomarker analysis.

2.2. Analytical methods

Height, weight (body mass index (BMI) calculated), total body fat percentage and waist circumference were measured by standard procedures. Blood pressure (average of two readings)
was measured using a mercury sphygmomanometer after resting for at least 5 min. Biochemical measures (glucose, HbA1c, lipid profile) were measured using an auto-analyzer (COBAS – Integra, Germany) with appropriate quality control measures. Plasma insulin was measured by an electrochemiluminescence assay using an Elesys Cobas e411 auto-analyzer (Roche diagnostics, Mannheim, Germany; CV < 3%; detection range: 1.39–6945 pmol/l). Insulin resistance (IR) was calculated using the Homeostasis model assessment using the formula: (fasting insulin × fasting glucose)/22.5 [15]. The insulinogenic index (IGI) was calculated as the ratio of the change in insulin to the change in glucose from 0 to 30 min following the oral glucose load (ΔI_{0–30}/ΔG_{0–30}) [16].

### 2.3. Assays of adipokines

Plasma leptin was measured using sandwich enzyme-linked immunosorbent assay (ELISA) (DBC diagnostics, Canada). The intra- and interassay coefficients of variation (CVs) were <5.5% and <7%, respectively, for sample concentration range of 1–100 ng/ml. The detection limit was 1 ng/ml. Plasma adiponectin was assayed using solid phase ELISA (Organum, Finland). The intra- and interassay CVs were <10% and <12%, respectively. The detection limit was <0.185 ng/ml. IL-6 was assayed using a sandwich ELISA (eBioscience, San Diego, CA). The intra- and interassay CVs were each <10%. All the measurements were carried out in freshly thawed fasting plasma samples stored at −80°C.

### 2.4. Statistical analyses

#### 2.4.1. Sample size calculations

2.4.1.1. Adiponectin. The Indian Diabetes Prevention Programme-1 (IDPP-1) [17], and the Japanese Funagata Study [18] found a strong inverse association between adiponectin and incident T2DM. In the IDPP-1, the mean baseline adiponectin was lower in the T2DM as compared with the normoglycaemic group (11.3 ± 5.5 vs. 16.7 ± 7.6 μg/ml). With 25 individuals in each group, this expected difference and standard deviations, is demonstrated as significant at \( P < 0.05 \) and with 80% power.

2.4.1.2. IL-6. The European Prospective Investigation into Cancer and Nutrition (EPI) – Potsdam study [19] demonstrated that IL-6 was elevated in T2DM compared with controls. With 76 individuals in each group, the expected difference with standard deviations (1.67 ± 1.59 vs. 2.45 ± 1.80 pg/ml [19], is demonstrated as significant at \( P < 0.05 \) and 80% power for IL-6.

2.4.1.3. Leptin. The British Regional Heart Study [8], demonstrated that leptin levels were higher in persons with T2DM than in the non-diabetic group (T2DM: 14.3 (inter quartile range (IQR): 10.2–21.9); normal: 8.93 (IQR: 5.6–14.1); assumed standard deviation: 11.5; \( P < 0.0001 \)). With 73 individuals in each group, and with the standard deviation, the expected difference is found to be significant at 5% level and 80% power.

For this study, 76 cases and 71 controls were included for the biomarker estimations.

### 2.5. Statistical methods

Normally distributed variables were expressed as mean ± SD and compared using two-tailed t-test. Non-parametric variables were expressed as median (IQR) and were compared using Mann–Whitney test. For correlation and regression analyses, non-normally distributed parameters were transformed to natural logarithmic scale. Pearson correlation was performed to evaluate the association of biomarkers with surrogate insulin measures and cardiovascular risk factors. Associations of adiponectin, IL-6 and leptin with incident diabetes were calculated using logistic regression analyses. Each biomarker was tested separately in three models: (i) unadjusted model; (ii) model-1, adjusted for intervention, family history of diabetes, baseline age and BMI; and (iii) model-2, adjusted for model-1+ HbA1c, HOME-IR and insulinogenic index. The biomarkers were log transformed and centred so that odds ratio (OR) for a 1-SD change was computed. The predictive power of each biomarker and HbA1c for conversion to diabetes was assessed with receiver-operating-characteristic (ROC) curves. The area under the curve (AUC) of the ROC and the 95% confidence interval (CI) were calculated by the Delong method to evaluate the diagnostic utility of the marker for prediction of diabetes. The optimal cut-off point of each marker was estimated by calculating the Youden index. Its specificity and sensitivity were calculated using that cut-off. The positive likelihood ratio was calculated using the formula: sensitivity/(1-specificity). In these analyses, the predictive ability of individual biomarker (adiponectin, IL-6 and leptin) was compared against HbA1c. We have also explored the predictive value of the combination of each biomarker with HbA1c and in comparison with the predictive value of HbA1c alone (reference model). Statistical analysis was performed using STATA version 13.1 (Stata Corp, Texas, USA).

### 3. Results

Baseline clinical characteristics of study participants according to the glycaemic outcomes at the end of the study period are shown in Table 1. The baseline diastolic blood pressure in those who developed diabetes was higher compared to non-progressors (\( P = 0.046 \)). At the end of the follow-up the levels of systolic and diastolic blood pressure improved in individuals who regressed to normal (systolic: \( P = 0.0039 \); diastolic: \( P = 0.0059 \)) compared to non-diabetic individuals. Baseline glycaemic markers (fasting and 2 h plasma glucose and HbA1c) and triglycerides levels (\( P = 0.022 \)) were higher in those who developed diabetes compared with non-progressors (\( P < 0.0001 \)). As expected, the levels of glycaemic measures and triglycerides were significantly higher among the cases at the end of the follow-up, progressors were more insulin resistant (\( P < 0.0001 \)) and had decreased beta cell function (\( P < 0.0001 \) at baseline and during follow-up (HOMA-IR: \( P = 0.0046; \) IGI: \( P < 0.0001 \)).

The baseline median value of adiponectin was 30% lower in those who converted to T2DM compared with those who did not convert (converters: 11.5 (IQR: 8.6–15.0) vs. non-converters: 16.4 (IQR: 11.6–21.4); \( P < 0.0001 \)). The level of IL-6 was higher by...
181% in the converters vs. non-converters ([5.3 (IQR: 4.7–12.4) vs. 14.9 (IQR: 5.8–24.9); P < 0.0001]). Levels of leptin were similar in the two groups (8.9 (IQR: 6.8–16.5) vs. 12.3 (IQR: 8.0–17.4); P = 0.170).

**Table 2** shows the correlations of the adipokines with metabolic and anthropometric risk factors. IL-6 and leptin were positively correlated and adiponectin was inversely correlated with BMI. IL-6 and leptin showed positive correlation with waist circumference. Adiponectin was inversely correlated and leptin was positively correlated with HOMA-IR. There was no association between IL-6 and HOMA-IR. Leptin and HbA1c were not significantly correlated.

In unadjusted logistic regression models, adiponectin (OR: 0.509 [0.351–0.736]; P < 0.0001) and IL-6 (OR: 1.999 [95%CI: 1.394–2.865]; P < 0.0001) were significantly associated with risk of developing diabetes. Leptin (OR: 1.249 [95%CI: 0.896–1.741]; P = 0.170) did not show significant association with diabetes (Table 3). The associations of adiponectin (OR: 0.550 [95%CI: 0.334–0.908]; P = 0.019) and IL-6 (OR: 2.27 [95%CI: 1.398–3.691]; P < 0.001) persisted even after adjusting for demographic and anthropometric variables, family history of diabetes (model 1), and baseline HbA1c, HOMA-IR and insulinogenic index (model 2).

**Table 4** shows the changes in predictive power of the models when the adipokines were combined with HbA1c (base model). The AUC of HbA1c, adiponectin and IL-6 were 0.725 (95%CI: 0.648–0.798), 0.695 (95%CI: 0.613–0.768) and 0.688 (95%CI: 0.606–0.761), respectively. Addition of adiponectin to HbA1c in the model improved the AUC marginally (ΔAUC: 0.0619; P = 0.0251; AUC: 0.787(0.714–0.852); sensitivity (%): 77.5; specificity (%): 61.8). Though, IL-6 was a significant predictor of incident diabetes, combining it with HbA1c did not enhance the predictive power. The ROC of combination of adiponectin and IL-6 (AUC: 0.736 [95%CI: 0.656–0.804]) was not higher than that of HbA1c alone (P = 0.864).

### 4. Discussion

This nested case-control analysis in a cohort of middle-aged Asian Indian men with prediabetes showed that low levels of adiponectin and high levels of IL-6 at baseline were significantly associated with T2DM independent of age, BMI, levels of insulin resistance and beta-cell function. This observation is consistent with our previous finding that low adiponectin is a strong predictive marker of incident T2DM in Asian Indians [17]. A recent meta-analysis by Li et al. [7] has shown that lower adiponectin levels are independently associated with incident diabetes in populations of varied ethnicity.

The present study showed a moderate association between adiponectin and HOMA-IR in men with IGT. A similar association has been reported in Asian Indian adult men and women [20]. In a previous study in non-diabetic teenagers we found no association between adiponectin and HOMA-IR.
[21]. The relationship between adiponectin and insulin sensitivity varies among different ethnic groups. In a multi-ethnic population based study, levels of adiponectin correlated inversely with insulin resistance only in white populations whilst no such association was observed in black and south Asian populations [22].

Previous studies have demonstrated that higher levels of IL-6 are associated with the increased risk of diabetes, supporting an association of chronic inflammation with development of diabetes in multi ethnic populations [11,12,23]. Chronic low-grade systemic inflammation could mediate diabetogenesis via insulin resistance [24] but other mechanisms have also been suggested [11,12,23,25]. Positive associations of IL-6 with BMI and T2DM were noted in our cohort, however these associations were not mediated through insulin resistance. A comprehensive review by Kristiansen and Mandrup-Poulsen [26] postulated that chronically elevated IL-6 might contribute to the development of T2DM through mechanisms involving altered insulin signaling in hepatocytes/adipocytes and also impaired energy regulation in the central nervous system. The British Regional Health Study [8] in elderly men also reported findings similar to ours indicating that the association of IL-6 with diabetes was independent of insulin resistance. More detailed studies are warranted to analyse the causative link of IL-6 with diabetes.

Importantly, we found that the combination of adiponectin with HbA1c improved the predictive power of HbA1c only marginally. Although IL-6 and adiponectin were independently associated with diabetes the combination of both was not superior to that of HbA1c in predicting incident diabetes. This demonstrates that these adipokine biomarkers may offer only marginal improvement in the prediction of diabetes when compared with the conventional glycaemic markers such as HbA1c. Salomaa et al. [27] noted that adding the novel biomarkers such as adiponectin, apolipoprotein B, interleukin 1-receptor A and ferritin, to the classical risk factors including

| Table 2 - Correlations between adipokines with anthropometric and biochemical variables. |
|----------------|----------------|----------------|
| Variables       | Adiponectin   | IL-6          | Leptin       |
| Adiponectin (µg/ml) | -              | -0.057        | -0.121       |
| IL-6 (pmol/ml)   | -0.057        | -              | 0.277        |
| Leptin (ng/ml)   | -0.121        | -0.277        | -            |
| Age (years)      | 0.166         | -0.065        | 0.024        |
| Body mass index (kg/m²) | -0.238       | 0.169         | 0.433        |
| Waist circumference (cm) | -0.126       | 0.174         | 0.349        |
| Fat%             | -0.052        | 0.221         | 0.275        |
| Systolic blood pressure (mm Hg) | -0.114       | -0.006        | 0.146        |
| Diastolic blood pressure (mm Hg) | -0.084       | 0.139         | 0.228        |
| Fasting glucose (mmol/l) | -0.192       | 0.119         | 0.221        |
| 2-h glucose (mmol/l) | -0.154       | 0.194         | 0.280        |
| HbA1c (%)        | -0.115        | 0.027         | 0.153        |
| Triglycerides (mmol/l) | -0.008       | 0.045         | 0.154        |
| HDL cholesterol (mmol/l) | 0.234        | 0.068         | 0.063        |
| HOMA-IR           | -0.211        | 0.080         | 0.222        |
| Insuliongenic index (pmol/mmol) | 0.088       | -0.153       | 0.185        |

IL-6: interleukin 6. * Log transformed. 1 P < 0.01. 2 P < 0.001.

| Table 3 - Results of logistic regression analyses. Adjusted relative risk (OR) of incident type 2 diabetes for adiponectin, IL-6 and leptin. |
|----------------|----------------|----------------|
| Variables      | β (se) OR [95%CI] | P value |
| Adiponectin    | Unadjusted -0.676 (0.189) 0.509 [0.351-0.736] | <0.0001 |
|                 | Model-1 -0.646 (0.199) 0.524 [0.355-0.774] | 0.001   |
|                 | Model-2 -0.597 (0.255) 0.550 [0.334-0.908] | 0.019   |
| IL-6           | Unadjusted 0.693 (0.184) 1.999 [1.394-2.865] | <0.0001 |
|                 | Model-1 0.703 (0.190) 2.018 [1.393-2.931] | <0.0001 |
|                 | Model-2 0.820 (0.246) 2.27 [1.398-3.691] | 0.001   |
| Leptin         | Unadjusted 0.222 (0.170) 1.249 [0.896-1.741] | 0.190   |

Dependent variable: diabetes vs. others. Model 1 adjusted for baseline age, allocation group, family history of diabetes and BMI; Model 2 adjusted for variables in Model 1 + baseline HbA1c, HOMAIR and insulonigenic index. Results for continuous variables are odd ratios for a 1-SD increase of the log-transformed variable. Leptin did not show an association with incident diabetes in an unadjusted analysis. Hence, an adjusted model was not explored.

| Table 4 - Area under the receiver operating characteristics curve and predictabilities of multiple markers for progression of diabetes. |
|----------------|----------------|----------------|
| Variables      | ROC area (se) | Sensitivity (%) | Specificity (%) | LR+ Incremental AUC | Chi square value | Pr > Chi square |
| HbA1c          | 0.725 (0.648-0.798) | 77.5 | 57.9 | 1.84 Ref | Ref | 0.5692 |
| IL-6           | 0.688 (0.606-0.761) | 69.0 | 65.8 | 2.02 -0.037 | 0.32 | 0.6901 |
| Adiponectin    | 0.695 (0.613-0.768) | 67.6 | 63.2 | 1.84 -0.030 | 0.28 | 0.6901 |
| HbA1c + IL-6   | 0.777 (0.699-0.842) | 77.5 | 60.5 | 1.96 0.052 | 3.6584 | 0.0558 |
| HbA1c + adiponectin | 0.787 (0.714-0.852) | 77.5 | 61.8 | 2.03 0.062 | 5.0162 | 0.0251 |
| IL-6 + adiponectin | 0.736 (0.656-0.804) | 73.2 | 64.5 | 2.06 0.011 | 0.0300 | 0.8624 |

AUC: area-under-curve; CI: confidence interval; IL-6: interleukin-6; LR+: positive likelihood ratio. a: HbA1c is the base model; b: P value was for comparing the AUC between base model (HbA1c) and additional models with multiple markers (HbA1c+ adiponectin or IL6 and adiponectin + IL6).
age, BMI, sex, lipid profile, systolic blood pressure, antihypertensive medication, current smoking, blood glucose, and history of cardiovascular disease improved the predictive power only marginally for T2DM in high risk middle aged Finnish population.

In our cohort, leptin did not show an association with T2DM. The findings on the association of leptin with diabetes had been contradictory. Some studies showed direct associations between leptin and diabetes in multi-ethnic populations [8,9,28,29] while another study, showed no association between leptin and diabetes [30,31]. In fact, much of the association between leptin and incident diabetes could be accounted for by obesity and insulin resistance [31]. In the Atherosclerosis Risk in Communities study [9], high leptin levels adjusted for demographic variables showed an increased risk of diabetes (HR: 3.9 [95% CI 2.6–5.6]) but, after adjusting for obesity indices, fasting insulin, inflammation score, hypertension, triglycerides, adiponectin and high levels of leptin predicted a lower diabetes risk (HR = 0.40, 95% CI 0.23–0.67). Therefore, further studies are required to explore the link between leptin and diabetes.

Our study has a few limitations. Firstly, the sample size of the study was small. However, the study design was adequately powered to detect the association with diabetes. Secondly, the study was done only in men and therefore the relevance of the findings in women needs to be ascertained. Thirdly, though we had included a few important biomarkers we might have missed out several other potential candidates such as serum lipoprotein (Lp) (a) concentrations [32], C-reactive protein [8,11,12], markers of endothelial dysfunction [33] and oxidative stress.

To summarise, we have demonstrated that adiponectin and IL-6 are independently associated with incident diabetes. However, the predictive power of a simple glycaemic marker, HbA1c, is not enhanced by combining it with these adipokines. Study of these biomarkers may have a role in understanding the pathogenesis of T2DM but are unlikely to serve as simple tools to predict future diabetes in a non-research setting.

Conflict of interest

None declared.

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Authors’ contributions

Vinitha R: researched data, contributed to discussion, wrote manuscript, reviewed/edited manuscript. Ram J: researched data, contributed to discussion, wrote manuscript, reviewed/edited manuscript. Snehalatha C: researched data, contributed to discussion, wrote manuscript, reviewed/edited manuscript. Nanditha A: contributed to discussion, reviewed/edited manuscript. Arun R: contributed to discussion, reviewed/edited manuscript. Samith A Shetty: contributed to discussion, reviewed/edited manuscript. Ian F Godland: contributed to discussion, reviewed/edited manuscript. DG Johnston: researched data, contributed to discussion, wrote manuscript, reviewed/edited manuscript. Ramachandran A: researched data, contributed to discussion, wrote manuscript, reviewed/edited manuscript.

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