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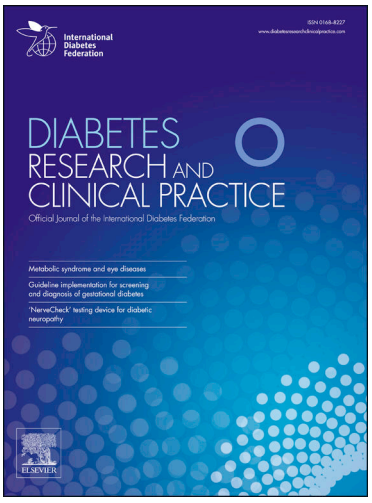

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Evaluating the 1-h Post-Load Glucose Level to Predict Future Type 2 Diabetes

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2894 words

2 tables

3 figures

Abstract

Aims

To evaluate the predictive ability of 2-h post-load glucose level in addition to fasting and 1-h glucose levels in predicting the risk of type 2 diabetes.

Methods

We examined a prospective population-based cohort study of 654 subjects without type 2 diabetes at baseline. All subjects underwent an oral glucose tolerance test (OGTT), with measurement of glucose at 0, 60, and 120 min at baseline, and after 12 years in a follow-up survey. We evaluated the predictive properties of fasting, 1- and 2-h post-load glucose levels by comparing the areas under the receiver-operating characteristic (ROC) curve.

Results

We found that 2-h glucose concentration in the prediction model with fasting and 1-h glucose levels did not significantly increase the predictability of type 2 diabetes compared to a model only including fasting and 1-h glucose levels (AUC 0.83 vs. AUC 0.82, respectively; p=0.23). The area under the ROC curve was the largest for 1-h glucose level (AUC 0.81), compared to fasting (AUC 0.71; p<0.01) and 2-h glucose levels (AUC 0.72; p=0.01).

Conclusions

Adding 2-h glucose to the model with fasting and 1-h glucose levels did not improve the predictability of new onset type 2 diabetes.

Keywords: OGTT, type 2 diabetes, 1-hour post-load glucose, prevention

1. Introduction

Type 2 diabetes is a progressive disease associated with cardiovascular and microvascular complications [1]. The early identification of individuals at high risk of developing type 2 diabetes is important given that factors such as lifestyle interventions have proven to be successful in the prevention of the disease at this stage [2-4]. So far, impaired fasting glucose (IFG) and increased 2-h post-load glucose in an oral glucose tolerance test (OGTT) have been the standard methods for identifying high-risk individuals [5].

In the past decade, population-based studies have shown that a 1-hour plasma glucose (1-h PG) level in an OGTT predicts type 2 diabetes even more effectively than fasting or 2-hour plasma glucose (2-h PG) levels [6-14]. It has been consistently reported that 1-h PG also predicts diabetic complications and mortality to at least a similar level to that of 2-h PG [11, 15-18] and, therefore, the 1-h PG level has been considered to be an alternative time point in an OGTT [12, 14, 19]. In addition, there has been some discussion regarding the replacement of 2-h PG with 1-h PG in order to better identify high-risk individuals [19, 20].

Our primary aim was to evaluate whether or not the 2-h PG level in the model including fasting and 1-h PG levels provides any additional benefit in predicting type 2 diabetes compared to a model only including fasting and 1-h PG levels in an age-based cohort with a comparison of characteristics of both sexes. Secondly, we also sought to confirm the previous findings concerning the value of 1-h PG in this context.

2. Materials and methods

2.1. Study design

Oulu45 is a prospective, population-based cohort study consisting of individuals born in 1945. The Ethics Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland approved the study protocol following the principles of the Declaration of Helsinki.

The study population consisted of 1,332 people living in the city of Oulu in northern Finland on 31 December 2001. The baseline clinical examination, including a standard 75-g OGTT, was carried out in 2001-2003. Finally, 993 individuals participated in baseline examinations and the participant rate was 74.5 %. All previous participants who were still alive 12 years later were invited to a follow-up study carried out in 2013-2015 in Oulu, and data was received from 714 subjects (71.9% coverage of baseline participants). The mean follow-up time was 12.1 ± 0.5 years. In this study, we also excluded the subjects with self-reported type 2 diabetes or a type 2 diabetes diagnosis based on OGTT glucose values in accordance with the World Health Organization criteria (1999) at baseline [21]. The complete glucose data for this study was available for 654 participants, consisting of 274 men and 380 women.

2.2. The definition of variables and outcomes

The standard 75-g OGTT was performed and glucose levels were determined at 0, 60, and 120 min. The diagnosis of type 2 diabetes was based on WHO criteria (1999) and two separate exceeding threshold values were required for the diagnosis. Fasting glucose levels were classified after an overnight 12-hour fast. At baseline, the glucose values were determined from the whole blood, in accordance with the previous clinical practice in Finland [33]. Because the glucose measures differ between the whole blood and venous plasma, we used a correction factor of 1.11 to equate the baseline fasting blood glucose to plasma glucose values [22]. The fasting and 2-hour glucose threshold values were as follows: normal glucose tolerance (NGT)

when the fasting plasma glucose was < 6.1 mmol/L and the 2-h plasma glucose was < 7.8 mmol/L and the screen detected diabetes mellitus when the fasting plasma glucose was ≥ 7.0 mmol/L or the 2-h plasma glucose was ≥ 11.1 mmol/L [21].

The baseline examination included fasting serum lipid values, which were analysed in a local quality-controlled standard laboratory. Blood pressure was measured by a nurse using standard techniques and was based on an average of two seated blood pressure measurements. The weight and the height of the participants were determined in light clothing and the body mass index (BMI) was calculated as weight (kilograms) divided by height (metres) squared. The waist circumference was measured at the midpoint between the iliac crest and the lowest rib, and the hip circumference at the maximum protrusion. All measurements were collected at baseline and after the 12-year follow-up. The family history of type 2 diabetes was not available.

2.3. Statistical Methods

Subject characteristics were described as means and standard deviations (SD) or as counts and proportions. The Student's t-test was used to compare continuous variables, and, in the case of categorical variables, Pearson's Chi-square test or Fisher's exact test were used where appropriate. The receiver operating characteristic (ROC) curve was applied in order to determine the cut-off points at which the optimal sensitivity and specificity of the glucose tests (fasting glucose, 1-hour PG and 2-hour PG) were achieved. Optimal sensitivity and specificity were defined as those yielding the minimum value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$. The area under the ROC-curve (AUC) was used to compare the predictive ability of the glucose tests. The ROC curves were also generated to compare the predictive ability of two logistic regression models, which were applied in order to predict diabetes. The first model included

fasting glucose and 1-hour PG tests, and the second model included the first model plus a 2-hour PG test as predictors. The analyses were carried out with IBM SPSS Statistics 23.0 (Armonk, NY: IBM Corp.) and MedCalc for Windows, version 17.9.7 (MedCalc Software, Ostend, Belgium). A two-sided *P* value was used, and results were considered statistically significant when $P < 0.05$.

3. Results

Table 1 presents the characteristics of our study group at baseline and at the 12-year follow-up survey by sex (274 men and 380 women). The study population consisted of individuals born in 1945. The mean age of the participants was 56.8 ± 0.5 years at baseline in 2001-2003 and 68.9 ± 0.6 years in the follow-up survey in 2015. At baseline, hip circumference and LDL cholesterol did not differ significantly between sexes. The BMI, waist circumference, waist-hip ratio, total cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, fasting, and 1-h post-load glucose levels were, however, higher among men and the HDL and 2-h post load glucose level among women ($p < 0.02$ for all comparisons). During the follow-up survey, such sex differences were not seen in BMI, diastolic blood pressure, triglycerides, and 2-h post-load glucose level, but hip circumference and LDL cholesterol were higher among women than in men. During the 12-year follow-up survey, 30 (11%) men and 30 (8%) women reported being diagnosed with type 2 diabetes in the health care system. In addition, according to the OGTT at the 12-year follow-up survey, 31 (11%) men and 16 (4%) women were diagnosed with type 2 diabetes (Table 1).

The baseline characteristics of the study population of men and women subdivided according to the incident diabetes are listed in Table 2. BMI, hip circumference, waist circumference,

waist-hip ratio, systolic blood pressure, triglycerides, HDL cholesterol, and plasma glucose levels were significantly higher among participants of both sexes who developed type 2 diabetes during the follow-up period ($p < 0.05$ for all comparisons). In addition, women who were diagnosed with type 2 diabetes had significantly higher diastolic blood pressure at baseline ($p < 0.05$) (Table 2).

In Figure 1, the area under the ROC curve was the greatest for the 1-h PG level (AUC 0.81; 95% CI 0.76-0.86), being lower for fasting (AUC 0.71; 95% CI 0.66-0.77, $p < 0.01$ between fasting and 1-h PG) and 2-h PG (AUC 0.72; 95% CI 0.66-0.79, $p = 0.01$ between 1-h and 2-h PG). The optimal cut-off point for fasting glucose when predicting type 2 diabetes was 5.5 mmol/L, for 1-h PG 8.9 mmol/L and 6.8 mmol/L for 2-h PG (Fig. 1). After evaluating both sexes separately, only slight differences were observed between men and women. The optimal cut-off point of fasting glucose for men was 5.7 mmol/L (AUC 0.74; 95% CI 0.66-0.81), and 5.4 mmol/L (AUC 0.66; 95% CI 0.57-0.75, $p = 0.21$) for women. The 1-h PG for men was 8.9 mmol/L (AUC 0.78; 95% CI 0.72-0.85), and 8.6 mmol/L (AUC 0.82; 95% CI 0.74-0.89, $p = 0.55$) for women. The 2-h PG for men was 6.4 mmol/L (AUC 0.70; 95% CI 0.61-0.79) and 6.8 mmol/L (AUC 0.77; 95% CI 0.68-0.86, $p = 0.28$) for women. When combining fasting and 1-h PG, the area under the ROC curve was 0.82 (95% CI 0.77-0.87), and when adding the 2-h PG level to this model, there was not a statistically significant increase in the area under the ROC curve (AUC 0.83; 95% CI 0.79-0.88, $p = 0.23$) (Fig. 2). In the further illustration, participants using angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-II-receptor blockers (sartans), HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors (statins), beta-blockers, estrogen-progestins (hormonal replacement therapy), or steroids have somewhat more new-onset type 2 diabetes during the follow-up (60.7% vs 50.5%, $p = 0.051$). Adjustment with all agents known to influence glucose homeostasis did not, however, affect the outcomes.

The Venn diagram (Fig. 3) illustrates the distribution of subjects with new onset type 2 diabetes predicted by 1-h PG (with a cut-off point of 8.9 mmol/L) and 2-h PG (with a cut-off point of 6.8 mmol/L) at baseline. In total, 1-h PG with a cut-off point of 8.9 mmol/L predicted 76.6% (82/107), whereas 2-h PG with a cut-off point of 6.8 mmol/L predicted 62.6% (67/107) of the new cases of type 2 diabetes. In addition, 12.1% (13/107) of new onset type 2 diabetes were only predicted by 2-h PG, whereas 26.2% (28/107) were only predicted by 1-h PG. Eleven percent (12/107) of new onset type 2 diabetes could not be predicted with these cut-off points of 1- and 2-h PG. Nevertheless, these individuals had the greatest mean change in BMI (+3.5 kg/m^2) when compared to others (+0.2 kg/m^2; 3.5 vs 0.2, $p < 0.001$) who developed type 2 diabetes during the 12-year follow-up.

When fasting glucose level was included in the evaluations, the 2-h PG level revealed that 8.4% (9/107) of individuals were not identified as being at risk of developing type 2 diabetes by fasting or 1-h PG levels. Of this 8.4%, six were females and three males; however, their waist circumference grew a median of 11.0 cm during the follow-up period. In contrast, fasting and 1-h PG levels jointly revealed 86.9% (93/107) of the individuals who developed type 2 diabetes during the follow-up period (Fig. 3).

4. Discussion

In this population-based study we found that the presence of 2-h PG concentration in the prediction model with fasting and a 1-h PG level did not significantly increase the predictability of type 2 diabetes compared to the model only including fasting and 1-h PG levels. Neither did we find any significant differences between the sexes. The predictive ability of 1-h PG was

greater than fasting or 2-h PG levels and fasting and 1-h PG levels jointly revealed 86.9% of the individuals who developed type 2 diabetes during the 12-year follow-up survey.

The strength of our study is that the diagnosis of new onset type 2 diabetes was based on the OGTT conducted in the 12-year follow-up survey and not solely on questionnaires or single fasting blood glucose values, which doubled the incidence of type 2 diabetes. Recent studies have, however, recorded type 2 diabetes via the national or local registers, potentially underestimating the incidence of type 2 diabetes during the follow-up period [10, 11]. In addition to ours, only a few studies have confirmed unclear diagnoses of type 2 diabetes with repetitive OGTT [6, 7, 21, 23].

Some potential limitations to our study should be acknowledged. First, participation in the research may motivate lifestyle changes. This could reduce the number of new onset type 2 diabetes in our study. Second, the definition of type 2 diabetes has changed in recent decades and HbA1c was not used as a diagnostic test at baseline in 2001-2003. Due to the lack of HbA1c determination, we were not able to evaluate the ability of HbA1c to predict type 2 diabetes in this context. In the present study, however, the accuracy of 1-h PG was found to be twice as great in detecting high-risk individuals than that of HbA1c [24]. Third, data regarding the menopausal stage or age of the participants was not available. A recent study of postmenopausal women found early menopause to be associated with a higher risk of future type 2 diabetes [25]. On basis of their age, we may reasonable assume that the majority of the female participants were postmenopausal. Finally, the family history of the participants was not available. This could have been relevant when evaluating the risk for type 2 diabetes.

Previous population-based cohorts have consistently demonstrated that the 1-h glucose level improves the predictability of new onset type 2 diabetes and is a better marker than fasting or 2-h PG levels [6-12], and this finding was supported by our study. Some previous cohort studies have mainly included middle-aged men [10, 11], whereas we also evaluated women in order to determine any possible differences between the sexes. Moreover, our study provides evidence for the predictability of 1-h PG among participants above 57 years of age. According to Abdul-Ghani et al. based on a North American population-based study, the determined optimal cut-off point of 1-h PG level was 8.6 mmol/L, which is also in accordance with our findings of 8.9 mmol/L [8].

As mentioned in the introduction before, lifestyle intervention and drug therapy have proven to be highly successful in reducing the incidence of type 2 diabetes among high risk individuals. Early detection of subjects at risk of developing type 2 diabetes is therefore critical [2-4]. According to our findings, the additional predictive power of 2-h PG level as a continuous variable was not significant. Consequently, limiting the OGTT to 1 hour should be considered. Our findings are in a line with the suggestions of the Botnia prospective study; i.e. that the combining fasting, 30min, 1-h PG, and 2-PG values did not improve the predictability of type 2 diabetes beyond 1-h PG alone [20]. By shortening the OGTT from 2-h to 1-h, significant cost savings can be achieved over time, however. Furthermore, it has been suggested that the 1-h PG level reflects the beta cell function and identifies individuals at risk of type 2 diabetes more effectively than HbA1c. This suggest that OGTT is a necessary screening tool in clinical practice [24].

After evaluating with the determined cut-off point, the 2-h PG level revealed that only 8.4% of individuals have not been found to be at risk of developing type 2 diabetes by fasting and 1-h

PG levels. The importance of the 2-h PG level in identifying patients with type 2 diabetes risk is therefore relatively low. However, according to 13 European cohorts, the 2-h PG values were shown to be higher in women than in men, and the prevalence of undiagnosed type 2 diabetes was based more on increased 2-h than the fasting glucose value, especially among women over the age of 70 [26]. In our study, six out of the nine of the participants who were identified only by the 2-h PG value to be at risk of developing type 2 diabetes were women. One possible explanation for this is that short people have a higher 2-h PG concentration than taller people in the OGTT [27]. In addition, it should also be noted that determination of one single individual diagnostic threshold can be artificial as it always excludes part of the sample at high risk of developing type 2 diabetes [28].

The majority of the previous studies have been conducted within the populations under 50 years of age (BOTNIA Study, mean age of the participants = 46 years; Malmö Preventive Project = 48 years; Southwestern Native American = 25 years) [6, 11, 29]. To the best of our knowledge, no other study includes participants with a mean age of 57 years or more at baseline and only one study includes both sexes at over 69 years of age in the follow-up survey [9]. We found the predictive ability of 1-h PG to be similar also among this population, too.

The theoretical basis for the more effective predictive value of 1-h glucose level compared to fasting or 2-h PG levels has been the subject of much discussion. The reduced beta cell function and increased insulin resistance are known to be the main pathophysiological mechanisms behind the development of type 2 diabetes [30-32]. Decreased glucose tolerance leads to changes in the shape of the glucose concentration curve during the OGTT [6, 9]. In individuals with an early stage of type 2 diabetes development, compensational insulin secretion can normalise the glucose concentration after a period of 2 hours but not after 1 hour [33].

In summary, our study findings support the hypotheses that the predictive value of 1-h PG level is greater than fasting or 2-h PG levels and adding 2-h PG to the prediction model of fasting and 1-h PG levels did not significantly increase the predictability of type 2 diabetes. Consequently, we highly recommend the use of 1-h PG as a prediction marker of type 2 diabetes in the OGTT of both sexes. Furthermore, the reduction of the OGTT time from two hours to one hour should be evaluated by additional comparative studies.

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Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement

A.E.S was the corresponding author. A.E.S, J.P.A, M.J.L and S.M.K-K designed the work, interpreted the data, and drafted and critically revised the manuscript. A.H.B designed the work, analysed and interpreted data, and drafted the manuscript. A.H.B also had access to the data and was responsible for the accuracy of the data analysis. All of the authors read and approved the final version of the manuscript.

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Table 1 - Characteristics of the study population by sex in 2003 and in 2015

	Men (2003)	Men (2015)	Women (2003)	Women (2015)	*P* values for difference between men and women at baseline	*P* values for difference between men and women at follow-up
Study population, n (%)	274 (42)	274 (42)	380 (58)	380 (58)		
BMI (kg/m^2)	27.3 ± 3.7	27.9 ± 4.3	26.4 ± 4.4	27.3 ± 5.0	0.004	0.11
Waist circumference (cm)	95.4 ± 10.5	99.8 ± 12.2	82.3 ± 11.3	89.4 ± 12.9	< 0.001	< 0.001
Hip circumference (cm)	100.8 ± 6.3	101.0 ± 8.3	101.1 ± 8.2	102.8 ± 10.2	0.70	0.01
Waist-hip ratio	0.95 ± 0.1	0.99 ± 0.1	0.81 ± 0.1	0.87 ± 0.1	< 0.001	< 0.001
Systolic blood pressure (mmHg)	139 ± 18	150 ± 19	135 ± 19	146 ± 21	0.01	0.018
Diastolic blood pressure (mmHg)	88 ± 10	87 ± 11	86 ± 11	86 ± 11	0.009	0.16
LDL cholesterol (mmol/L)	3.6 ± 0.9	3.1 ± 1.0	3.5 ± 0.8	3.6 ± 1.1	0.63	< 0.001
Triglycerides (mmol/L)	1.4 ± 0.8	1.3 ± 1.1	1.2 ± 0.5	1.2 ± 0.6	< 0.001	0.12
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.5 ± 0.4	1.9 ± 0.5	1.8 ± 0.4	< 0.001	< 0.001
Total cholesterol (mmol/L)	5.8 ± 0.9	4.9 ± 1.0	6.0 ± 0.9	5.7 ± 1.2	0.007	< 0.001
Fasting glucose (mmol/L)	5.4 ± 0.6	5.7 ± 0.8	5.3 ± 0.5	5.4 ± 0.7	< 0.001	< 0.001
1-h post-load glucose (mmol/L)	8.8 ± 2.3	10.2 ± 2.4	7.8 ± 1.8	9.3 ± 2.2	< 0.001	< 0.001
2-h post-load glucose (mmol/L)	6.2 ± 1.5	7.9 ± 2.0	6.4 ± 1.2	7.8 ± 1.6	0.016	0.40
Diabetes during the follow-up, n (%)	-	30 (11)	-	30 (8)		
Screen detected, n (%)	-	31 (11)	-	16 (4)		

Continuous variables are presented as mean ± SD. Categorical variables are presented as counts and percentages.

Table 2 - Characteristics of the study population of men and women subdivided according the incident diabetes at baseline

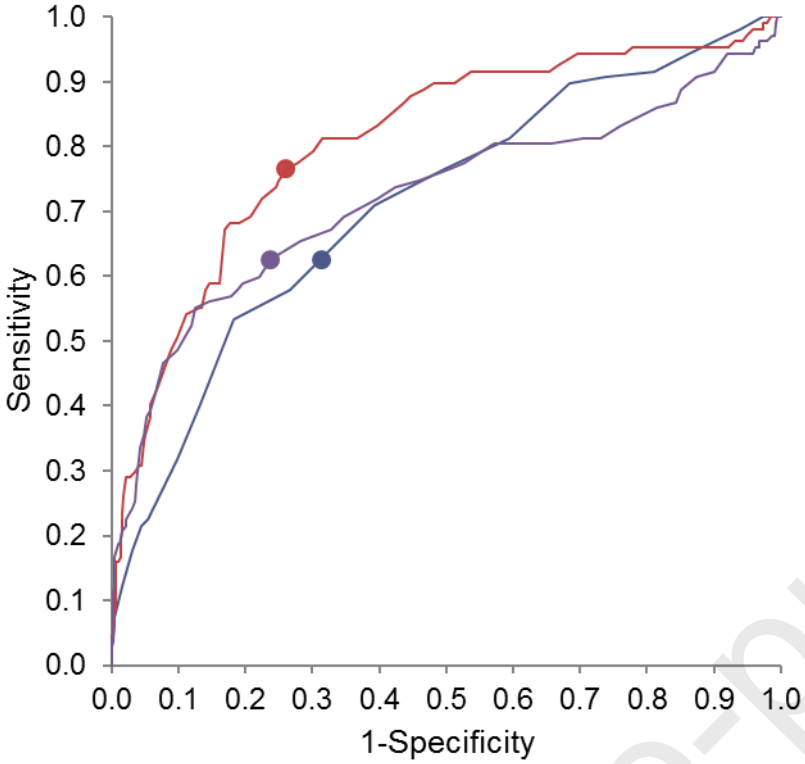
	Men without diabetes	Men with diabetes	*P* value between men with and without diabetes	Women without diabetes	Women with diabetes	*P* value between women with and without diabetes
Study population, n (%)	213 (80)	61 (20)		334 (88)	46 (12)	
BMI (kg/m^2)	26.6 ± 3.4	30.0 ± 3.6	< 0.001	26.0 ± 4.0	29.7 ± 5.3	< 0.001
Waist circumference (cm)	93.4 ± 9.8	102.5 ± 10.0	< 0.001	81.0 ± 10.5	92.0 ± 12.7	< 0.001
Hip circumference (cm)	99.9 ± 5.8	104.1 ± 7.0	< 0.001	100.4 ± 7.8	106.1 ± 9.3	< 0.001
Waist-hip ratio	0.93 ± 0.1	0.98 ± 0.1	< 0.001	0.81 ± 0.1	0.86 ± 0.1	< 0.001
Systolic blood pressure (mmHg)	137 ± 17	144 ± 20	0.01	134 ± 19	141 ± 19	0.02
Diastolic blood pressure (mmHg)	88 ± 11	90 ± 10	0.15	86 ± 11	90 ± 11	0.02
LDL cholesterol (mmol/L)	3.5 ± 0.8	3.6 ± 1.1	0.56	3.5 ± 0.8	3.6 ± 0.9	0.48
Triglycerides (mmol/L)	1.3 ± 0.7	1.9 ± 1.0	< 0.001	1.2 ± 0.5	1.6 ± 0.6	< 0.001
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.5 ± 0.4	0.01	1.9 ± 0.5	1.8 ± 0.5	0.04
Total cholesterol (mmol/L)	5.7 ± 0.8	5.9 ± 1.2	0.24	5.9 ± 0.9	6.1 ± 0.9	0.34
Fasting glucose (mmol/L)	5.3 ± 0.5	5.8 ± 0.6	< 0.001	5.2 ± 0.5	5.5 ± 0.5	< 0.001
1-h post-load glucose (mmol/L)	8.2 ± 2.0	10.7 ± 2.4	< 0.001	7.6 ± 1.6	9.9 ± 2.1	< 0.001
2-h post-load glucose (mmol/L)	5.9 ± 1.2	7.1 ± 1.9	< 0.001	6.2 ± 1.1	7.7 ± 1.5	< 0.001

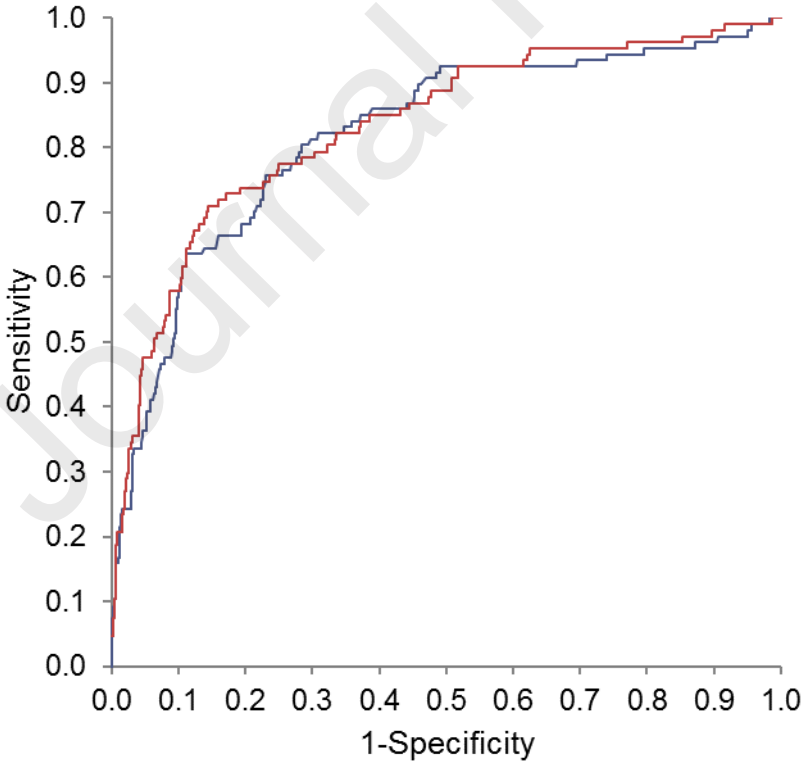
Continuous variables are presented as mean ± SD. Categorical variables are presented as counts and percentages.

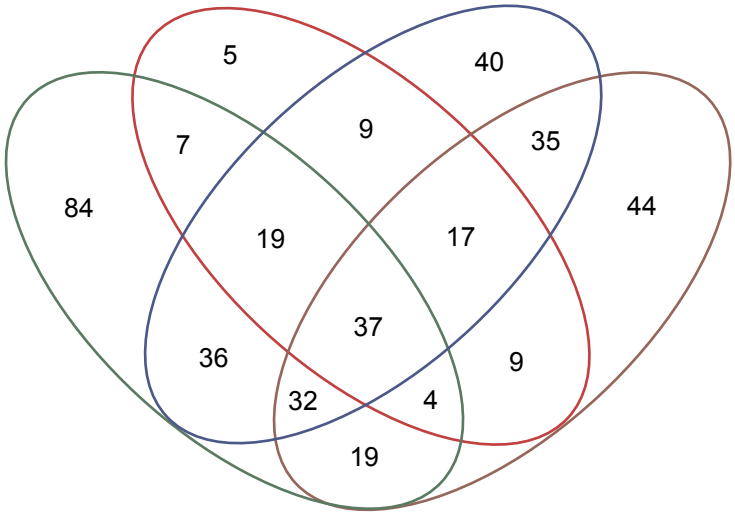
Figure 1 - Comparison between the areas under the Receiver Operating Characteristic (ROC) curve representing plasma glucose concentrations during the OGTT for prediction of type 2 diabetes in the future. The blue curve indicates the fasting glucose, red 1-h post-load glucose, and purple 2-h post-load glucose levels (n=654). Each point on the ROC curves represent the optimal cut-off values; 5.5 mmol/l (AUC 0.71), 8.9 mmol/l (AUC 0.81) and 6.8 mmol/l (AUC 0.72), respectively, ($p < 0.01$ between 0-h and 1-h glucose, $p = 0.01$ between 1-h and 2-h glucose).

Figure 2 - Comparison of Receiver Operating Characteristic (ROC) curves generated by two prediction models of diabetes (n=654). The first model (blue line) includes fasting glucose and 1-hour glucose tests (AUC 0.82; 95% CI 0.77-0.87), and the second model (red line) includes the first model plus 2-hour glucose test as predictors (AUC 0.83; 95% CI 0.79-0.88, p=0.23 between the areas under the ROC-curves (AUC)).

Figure 3 – Venn diagram representing the number of new onset type 2 diabetes predicted by optimal cut-off points (please see figure 1) of fasting, 1-hour and 2-hour plasma glucose levels during the 12-year follow-up (n=397). The red oval circle includes the participants diagnosed with new onset type 2 diabetes after baseline. The green circle illustrates the prevalence of participants with fasting plasma glucose ≥ 5.5 mmol/l, the blue circle with 1-h post-load glucose ≥ 8.9 mmol/l and the brown circle with 2-h post-load glucose ≥ 6.8 mmol/l at baseline.







Highlights

- Predictability of 1-h PG level was greater than fasting or 2-h PG levels
- Adding 2-h PG to fasting and 1-h PG levels did not increase the predictability
- Fasting and 1-h PG jointly found 87% of individuals who developed type 2 diabetes
- Our study recommends the use of 1-h PG level in an OGTT