Oral glucose tolerance test-based calculation identifies different glucose intolerance phenotypes within the impaired fasting glucose range

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ABSTRACT

Aims/Introduction: The conventional oral glucose tolerance test (OGTT) cannot detect future diabetics among isolated impaired fasting glucose (is-IFG) nor normal glucose tolerant (NGT) groups. By analyzing the relationship between fasting (FPG) and 2-h plasma glucose (2hPG), the present study identifies is-IFG subjects liable to worsening glucose homeostasis.

Materials and Methods: Oral glucose tolerance test was carried out in 619 patients suffering from obesity, hypertension or dyslipidemia, whose FPG was in the 100–125 mg/dL range. We calculated the percentage increment of 2hPG with respect to FPG (PG%) in these patients using the formula: ([2hPG – FPG] / FPG) × 100. Differences in β-cell function within is-IFG patients were assessed by estimated insulin sensitivity index (EISI), first-phase insulin release (1stPH) and 1stPH/EISI (1stPH_corrected).

Results: Diabetes was diagnosed in 69 patients (11.2%), combined IFG/IGT in 185 patients (29.9%) and is-IFG in 365 patients (58.9%). Is-IFG was subdivided into PG% tertile groups: the percentage of females increased from 25% in the lowest to 45.2% in the highest tertile (χ² = 18.7, P < 0.001). Moving from the lowest to the highest PG% tertile group, insulin and 2hPG concentrations rose, whereas FPG, EISI, and 1stPH_corrected decreased progressively and significantly. Furthermore, PG% correlated inversely with EISI (r = −0.44, P < 0.0001) and 1stPH_corrected (r = −0.38, P < 0.0001).

Conclusions: Oral glucose tolerance test does differentiate the great heterogeneity in metabolic disorders of patients with FPG 100–125 mg/dL. Furthermore, PG% can expand the diagnostic power of OGTT in the is-IFG range by distinguishing metabolic phenotypes very likely to herald different clinical risks.

INTRODUCTION

In 1997, the American Diabetes Association (ADA) introduced, in addition to the ‘impaired glucose tolerance’ (IGT), a new prediabetes category called ‘impaired fasting glucose’ (IFG), defined by a fasting plasma glucose (FPG) ranging from 110 to 125 mg/dL. In 2003, this range was modified again, lowering the FPG threshold to 100 mg/dL. As a direct consequence of the widening of the IFG range, a consistent proportion of subjects would be identified as affected by prediabetes without any confidence on the subsequent development of diabetes. Without the information derived from the 2-h plasma glucose (2hPG; the second hour glycermia during the oral glucose tolerance test [OGTT]), it is unwarranted to try to assess glucose homeostasis using FPG alone. Focusing on the IFG range, a series of questions arise. Do all IFG subjects share the same diabetes and/or cardiovascular risk? Only the OGTT allows us to differentiate between isolated IFG (2hPG < 140 mg/dL), combined IFG/IGT (2hPG ≥ 140 < 200 mg/dL) and type 2 diabetes.
diabetes (2hPG ≥ 200 mg/dL), whereas NGT is established by a FPG < 100, combined with a 2hPG < 140 mg/dL. The differences between these three categories of glucose intolerance stem from different pathophysiological mechanisms, resulting in different therapeutic approaches. It should be considered a priority to gather different information by accurately examining the isolated IFG range: a 2hPG < 140 mg/dL is prognostically more favorable than a 2hPG ≥ 140 mg/dL, as the latter value carries, in fact, remarkable clinical consequences. Furthermore, patients with isolated IFG, although sharing with normal glucose tolerance (NGT) subjects a normal 2hPG, behave quite differently. This difference can be explained by the heterogeneity in insulin sensitivity observed in IFG, possibly resulting in differences in cardiovascular risk and diabetes.

It might be possible that the OGTT suffers from severe limitations: being based on categorical FPG and 2hPG thresholds, its clinical relevance might not be adequate for preventive strategies, which, however, are necessary. If we look at bare facts, both in NGT and in the isolated IFG range, there are subjects more predisposed to developing diabetes, whereas the OGTT, conventionally interpreted, does not recognize them. Can the OGTT, in its actual ‘format’, yield additional information?

In the present study, we reaffirm the necessity of executing the OGTT in order to correctly stratify each distinctive type of glucose intolerance, especially to recognize subjects with isolated IFG. In addition, more thoroughly analyzing the interrelation-ship between 2hPG and FPG, we produce evidence that helps identify subjects with isolated IFG likely to undergo predictable alterations in glucose homeostasis.

MATERIALS AND METHODS

With exclusion of patients with known type 2 diabetes or affected by endocrine, liver and/or renal disease, or taking medications affecting glucose or insulin metabolism, such as β-blockers or diuretics, the present retrospective study was carried out on 1,798 subjects attending our metabolic facility because of obesity, hypertension or dyslipidemia from 2005 to 2011. Hypertension was defined as blood pressure ≥140 mmHg systolic and/or >90 mmHg diastolic. Of these 1,798 participants, 619 (34.4%) who were in the IFG range (FPG 100–125 mg/dL) by FPG measurement alone, while healthy by physical examination and routine laboratory exams, were included in the study. Their age was 56 ± 12.7 years, 319 were males (51.3%), 519 (83.9%) were affected by essential arterial hypertension, 363 (58.6%) were smokers (<10 cigarettes/day) and 218 of the 300 women (72.7%) were post-menopausal. In agreement with the ADA criteria, each IFG participant underwent an OGTT to accurately identify the type of glucose intolerance: IFG (2hPG < 140 mg/dL), combined IFG/IGT (2hPG ≥ 140 < 200 mg/dL) or type 2 diabetes (2hPG ≥ 200 mg/dL). FPG and 2hPG levels were measured by glucose oxidase; fasting plasma insulin (FPI) and 2-h plasma insulin (2hPI) by an immunometric ‘sandwich’ assay (Immulite 2000; Diagnostic Products, Los Angeles, CA, USA).

In participants with isolated IFG (is-IFG), we calculated the percentage increment of 2hPG with respect to FPG (PG%) using the formula: PG% = ([2hPG – FPG] / FPG) × 100. We divided the group of is-IFG participants into PG% tertiles to investigate possible differences in β-cell function previously shown in NGT participants. Using fasting and 2-h values of glucose and insulin, we calculated the estimated insulin sensitivity index (EISI) and the first-phase insulin release (1stPH), as described by Stumvoll. The generation of these indexes, validated by clamp techniques, was based on simple statistical methods using stepwise linear regression analysis and conceived for different sets of OGTT time-points. Among these indexes we selected those that use FPG, 2hPG, FPI and 2hPI. The actual formulas used were: EISI = 0.156 – 0.0000459 × 2hPI – 0.000321 × FPI – 0.00541 × 2hPG, and 1stPH = 2.032 + 4.681 × FPI – 135.0 × 2hPG + 0.995 × 2hPI + 27.99 × body mass index (BMI) – 269.1 × FPG, respectively. Because of the strong relationship between insulin sensitivity and insulin secretion, we obtained an estimated index of β-cell function by dividing 1stPH by EISI (indicated by the symbol 1stPH_corrected), which accounted for variations in insulin sensitivity. Like other OGTT-derived estimates of insulin response and insulin sensitivity used to show differences in β-cell function between glucose tolerance groups, we reported a progressive decline of 1stPH_corrected with worsening glucose homeostasis. This simply shows that the faltering insulin sensitivity is not being sufficiently compensated by increased insulin release with progressive glucose homeostasis derangement. To avoid negative results, we added two arbitrary numbers, 20 and 17, respectively to each calculated value of EISI and 1stPH. We want to stress the fact that the equations chosen were those that allowed us to calculate the indexes with the minimum of measurements and expenses, as our study is addressed to general medical care available to the largest number of facilities.

On the morning of OGTT execution, we calculated the BMI of each participants by dividing weight by the square of height (kg/m²), and measured waist circumference (WC) in cm, midway between the lowest rib and the iliac crest while standing. Data are presented as means ± standard deviations from the mean. Comparisons between groups were carried out by analysis of variance and post-hoc analysis of Tukey. Categorical variables were compared by Pearson’s χ²-test, while correlations between parameters were evaluated using Pearson’s correlation coefficients. Finally, regression analysis was carried out between changes in PG% and those of EISI and 1stPH. P < 0.05 was considered significant. Plasma insulin levels, EISI, 1stPH and 1stPH_corrected were non-normally distributed, and therefore were log-transformed before analysis. STAT 5.0 (Statistica Inc., Tulsa, OK, USA) was used for statistical analysis.

The present study was carried out according to the Helsinki declaration and approved by the ethical committee of the ‘Amedeo Avogadro’ University.
RESULTS

Following the 2003 ADA criteria, which rely exclusively on FPG, 34.4% (n = 619) of the 1,798 participants were identified as IFG; the remaining 1,083 participants with normal FPG (60.2%) and 96 (5.3%) with diabetes were excluded from the study. The OGTT carried out in IFG participants yielded the following results: 69 IFG participants (11.2%) were found to be affected by previously undiagnosed diabetes, 185 participants (29.9%) had combined IFG/IGT and 365 participants (58.9%) had is-IFG; this last group is the object of the present study, and could not have been identified without the OGTT that allowed the exclusion of those affected by diabetes and by the mixed IFG-IGT derangements.

After computing the PG% in the 365 is-IFG participants, we subdivided them into tertile groups. The PG% cut-off values were −6.8%, which separated the lowest from intermediate tertile, and 10%, which separated the intermediate from the highest tertile.

Table 1 shows the clinical features of the PG% tertile groups. There were no within-group differences in age, BMI, WC, percentage of smokers, participants with arterial hypertension and with BMI >30. Only the sex distribution was uneven, as the percentage of females varied significantly from 25% in the lowest to 45.2% in the highest PG% tertile group (χ² = 18.7, P < 0.001).

Table 2 shows the mean values ± SD of the derived OGTT data of each PG% tertile group. In the lowest PG% tertile group, FPG was significantly higher, whereas FPI was significantly lower in comparison with the highest tertile group. Proceeding from the lowest to the highest tertile group, both 2hPG and 2hPI rose progressively and significantly.

Contrary to the 1stPHI, both EISI and 1stPHI_corrected progressively and significantly decreased from the lowest to the highest tertile group.

Furthermore, considering these 365 is-IFG participants, we found significant negative correlations between the PG% and EISI (r = −0.44, P < 0.0001), and between PG% and 1stPHI_corrected (r = −0.38, P < 0.0001).

Finally, the regression equations between these same measurements were significant (PG% = 81.1–2.87 EISI and PG % = 69.3–8.34 1stPHI_corrected, P < 0.0001).

DISCUSSION

The major impact of the present results rests on the demonstration that it is useless to attempt to identify individuals at high risk for type 2 diabetes resorting exclusively to FPG measurement. The actual definition of IFG has broadened the prevalence of subjects labeled as affected by prediabetes and potentially susceptible to preventive treatments. Nevertheless, as reported by epidemiological data, the development of diabetes in IFG subjects varies widely, such that most of these will never develop diabetes. As its development requires a progressive increase in postprandial and FPG, it seems limiting to assess glucose homeostasis without the execution of OGTT, which affords additional information that should not be ignored.

The present data show that the 619 participants with FPG 100–125 mg/dL exhibited a wide heterogeneity in glucose homeostasis, such that they cannot be considered endowed with the same diabetes risk. In fact, with the execution of OGTT, an unforeseen 11.2% (n = 69) of these participants had diabetes already, 29.9% (n = 185) the combined IFG/IGT derangement, just 58.9% (n = 365) were affected by the isolated IFG.

Taken together, these data unequivocally show that the IFG range, characterized by different degrees of insulin sensitivity, insulin secretion and β-cell function, is far from being homogeneous: only the OGTT can specify each type of glucose intolerance and metabolic abnormality heralding distinct pathways to diabetes. Without this test, treatment will consequently be delayed, whereas its effectiveness is unanimously considered much higher the sooner it is started.

Furthermore, in the present study we focused our attention on isolated IFG subjects whose 2hPG was in the normal range (<140 mg/dL). Studies purporting to examine the gluco-regulatory physiology of subjects with isolated IFG are discrepant. Both normal and abnormal insulin sensitivity have been reported. Actually, isolated IFG seems to appear the prediabetes group in which insulin sensitivity varies more widely.

In the present study, we tested whether the PG% can recognize, in isolated IFG, different metabolic phenotypes endowed with specific derangements in glucose homeostasis. Considering that the faster post-load glucose (i.e., 2hPG) drops towards FPG, or the slower it rises, the more efficient is β-cell function,
Table 2 | Mean values ± standard deviations of oral glucose tolerance test-derived data of each percentage increment of 2-h plasma glucose tertile group

| Lower PG% tertile (n = 121) | Middle PG% tertile (n = 120) | Higher PG% tertile (n = 124) | Analysis of variance |
|-----------------------------|-----------------------------|-----------------------------|---------------------|
| FPG (mg/dL)                 | 108.6 ± 7.1                 | 108.1 ± 6.6                 | 106.3 ± 5.6*        | 4.7                  | <0.01 |
| 2hPG (mg/dL)                | 87.0 ± 12.3                 | 109.6 ± 7.9†               | 126.7 ± 8.6†       | 485.6                | <0.0001 |
| FPI (µU/mL)                 | 11.9 ± 6.3                  | 12.1 ± 6.2                 | 14.1 ± 7.8*        | 2.25                 | NS    |
| 2hPI (µU/mL)                | 49.8 ± 38.9                 | 66.2 ± 45.1*§              | 86.8 ± 70.3†       | 12.25                | <0.0001 |
| EISI × 100                  | 29.3 ± 2.1                  | 28.1 ± 2.2†               | 26.7 ± 3.1†        | 31.45                | <0.0001 |
| 1stPH/100                   | 29.8 ± 4.3                  | 29.3 ± 4.5                 | 30.4 ± 6.4         | 0.61                 | NS    |
| 1stPHcorrected             | 8.68 ± 0.78                 | 8.16 ± 0.72‡              | 7.94 ± 0.77‡       | 68.1                 | <0.0001 |

Data presented as means ± standard deviations of fasting plasma glucose (FPG), 2-h plasma glucose (2hPG), fasting plasma insulin (FPI), 2-h plasma insulin (2hPI), estimated insulin sensitivity index (EISI) multiplied by 100 to avoid a number lower than one, first phase insulin secretion (1stPH) divided by 100 to avoid large numbers, and 1stPHcorrected of each PG% tertile group. The analysis of variance is presented in the last two columns to the right. NS, not significant. *P < 0.05 vs lower PG% tertile group; †P < 0.0001 vs lower and middle tertile groups; ‡P < 0.0001 vs lower PG% tertile group; §P < 0.01 vs higher tertile group.

we recently proposed the simple calculation of PG% with the aim of testing the possibility to expand the clinical use of ‘standard’ OGTT16,24. In fact, exploring the NGT range, we previously reported a negative relationship between PG% and β-cell function: the lower the PG%, the better the β-cell function appears to be16. This notion seems substantiated by the San Antonio Heart Study15, where NGT subjects whose plasma glucose falls slowly to FPG levels during OGTT have a significant risk of progression to type 2 diabetes compared with NGT subjects whose plasma glucose values fall faster. This risk, related to an impaired insulin sensitivity and impaired β-cell function, can thus be rather accurately detected by the PG%. The results of the San Antonio Heart study can be equated to a provisional validation of PG% as a predictor of cardiovascular risk. It is understandable that even in apparently low-risk conditions, such as IFG, there could be a further stratification according to different insulin sensitivity conditions that the PG% can pinpoint.

Actually, in agreement with these data previously obtained in NGT subjects, the present study confirms then that the PG% can individuate different metabolic phenotypes within the is-IFG range: those with the higher PG% show unequivocal impairment of β-cell function.

In the lower PG% tertile group, we found that both 2hPG and 2hPI were significantly lower than those found in the higher tertile group. This means that the low post-load glycemic values, consistent with a low PG%, if not associated to high insulin values, are expression of a better insulin sensitivity. Insulin sensitivity, instead, progressively worsens with a rising PG%. In fact, in the higher PG% tertile group, we observed significant higher post-load glycemic values coupled to higher post-load insulin values. In essence, despite a wide availability of insulin concentrations, the finding of higher blood glucose values reflects an important impairment in insulin homeostasis. In addition, insulin secretion was not different among tertile groups: however, we found that the progressive increment of PG% is associated with a progressive decrement of insulin secretion when corrected for insulin sensitivity in order to obtain a surrogate marker of β-cell function23. Thus, the significantly negative correlation we have found between the PG% and the 1stPHcorrected can account for the great heterogeneity of insulin sensitivity reported by several studies carried out in the IFG range10–12,17.

Many authors support the notion that only the first hour value after oral glucose load is a marker of diabetic risk30,31. However, if we compute the PG% from the mean FPG and 2hPG values of 83 ± 6 and 109 ± 21 mg/dL of the San Antonio Heart Study and Botnia Study, we obtain 31.3%, which falls to 7.4% with mean FPG and 2hPG values of 81 ± 1 and 87 ± 11 mg/dL, respectively. Thus, PG% alone, computed from 2hPG, without intermediate glycemic values, is adequate to measure the risk even within NGT subjects. Examining in the same way the data of the IFG subjects, we obtained similar results. This supports the usefulness of using PG% in clinical practice.

Thus, we believe that the intermediate glycemic value proposed might be appropriate and useful, though unnecessary. Therefore, we suggest the clinical use of a new index, derived directly from standard OGTT, which reflects β-cell function, available without any additional burden while requiring only a simple mathematical calculation. This new index, the PG%, can expand, like in the NGT range, the diagnostic power of OGTT even in is-IFG range by distinguishing the different metabolic phenotypes heralding different clinical progressions. Our data show only the capability of PG% in detecting the different phenotypes, whereas its translation into effective prevention is inferred by studies of the literature that link these phenotypes to diabetic risk14,17,19,30,31. A direct confirmation that is-IFG subjects with high PG% are fraught with increased diabetic risk will have to await extended observational studies. Thus, the strength of the present study, which rests on the original proposal of a new OGTT-derived index, is limited by the indirect...
confirmation of the detection of metabolic risk. However, the present data make it possible to individuate beforehand the patients more likely to develop morbid events, thus allowing the planning of meaningful epidemiological trials.

It is likely that other indexes, such as the Matsuda index, based on plasma glucose and insulin concentration at times 0 and 120, might furnish equivalent information without resorting to the OGTT procedure. For instance, the Matsuda index calculated from the mean data of Table 2 is 4.22, 3.25 and 2.46, respectively for the three tertiles, strongly supporting our conclusions. However, the PG% has the advantage of being applicable to single patients, and of not requiring insulin measurements. Thus, the present study simply improves the information obtained with the worldwide acknowledged procedure of OGTT, implementing the physician’s skills with a very simple and low-cost calculation to potentiate prevention strategies.

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