

Searching For Prediabetes before Diabetes

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Abstract

Type 2 Diabetes Mellitus (T2DM) and pre diabetes prevalence is increasing worldwide at an alarming rate. Though many risk factors have been identified, the most appropriate strategy to identify when and who should undergo a more accurate screening, which could allow an earlier diagnosis and a more efficient prevention of complications, is still a matter of debate.

In this review we present data from a cohort of 2126 asymptomatic non diabetic subjects, who underwent an Oral Glucose Tolerance Test (OGTT). We have discussed our results sub-classifying our population according to the risk factors for diabetes development previously proposed by the American Diabetes Association.

According to our data, OGTT is able to identify a substantial proportion of subjects with prediabetic conditions who, if untreated, could progress to overt T2DM and potentially encounter serious health problems, even in non-at risk subgroups, such as subjects with a normal fasting glucose, who have a normal lipid profile and arterial pressure, who do not have a familiar history of diabetes and who do not fulfil classification criteria for metabolic syndrome.

Interestingly, a further proportion of subjects fulfil OGTT criteria for diagnosis of T2DM in each of these subgroups. Therefore, we believe that OGTT execution should be advocated as a screening test in asymptomatic populations to search prediabetes before diabetes.

Keywords: Type 2 diabetes mellitus; OGTT; Impaired fasting glucose (IFG); Impaired glucose tolerance (IGT)

Introduction

Type 2 diabetes mellitus (T2DM), strongly associated with microvascular and macrovascular complications, is increasing at an alarming rate worldwide [1] and, consequently, the estimated cost of its treatment, including that of related complications, is likely to increase dramatically [2].

The natural history of T2DM involves a rather long period, called prediabetes, in which defects in insulin sensitivity and secretion may be detected. Prediabetes, defined as impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), is a major risk factor for development of T2DM. In addition, IGT has been associated with an increased risk of cardiovascular morbidity and mortality.

Prospective studies have established that the implementation of lifestyle interventions and/or pharmacologic treatment can prevent/delay the onset of diabetes in high-risk subjects [3-6] resulting in a higher rate of diabetes remission, and/or in delayed need of diabetes medications in newly diagnosed subjects [7].

By the time T2DM is diagnosed, many patients already suffer from microvascular complications [7,8]; therefore, early recognition is critical. Strategies to identify individuals at increased risk of developing T2DM or affected by unknown diabetes do, indeed, limit complications and lower costs. How to plan these preventive strategies?

All clinical trials designed to investigate the possibility of delaying the onset of T2DM were focused on patients with IGT, or both IGT and IFG. IFG is defined as a fasting (at least 8 hours) plasma glucose (FPG) level ≥ 100 and < 126 mg/dl, whereas IGT as a glucose level ≥ 140 and < 200 mg/dl 2 hours after a 75-g oral glucose tolerance test (OGTT) [9].

Based on data from the National Health and Nutrition Examination Survey, the prevalence of subjects with prediabetes increased progressively from 1999 to 2010, reaching an alarming 36% in subjects older than 18 [10]; it is estimated that nearly 60% of patients with T2DM had prediabetes 5 years before diagnosis [11].

Thus, screening asymptomatic populations is appropriate, such that the American Diabetes Association (ADA) [8] suggests executing OGTT in individuals who are overweight (BMI ≥ 25) and have one or more of other risk factors such as age ≥ 45 years, family history of T2DM, habitual physical inactivity, particular ethnicity, previously identified IFG or IGT, history of gestational diabetes, hypertension, HDL-cholesterol ≤ 35 mg/dl and/or a triglyceride (TG) level ≥ 250 mg/dl, polycystic ovary syndrome, history of vascular disease [8].

These risk factors are so common that in very few individuals the OGTT would not be indicated, to the point that it should be performed much more frequently. However, this is not done as there is no uniform consensus on its usefulness [12,13]. OGTT is time consuming and unsatisfactorily reproducible [14]. This is the reason why ADA requires a second OGTT to confirm a diagnosis of diabetes and introduced the glycated haemoglobin (HbA1c) for diagnosing the alterations in glucose metabolism [15].

Almost half of patients remain undiagnosed because of the lack of symptoms [8,16]. This is an even more compelling reason to routinely perform OGTT, that detects both prediabetes, thus allowing a beneficial early treatment [3-7], and overt T2DM. In this opinion paper, we have reviewed the literature to verify the clinical impact of OGTT; we also report the results from a cohort of 2126 asymptomatic

non diabetic subjects attending our metabolic diseases clinic. We will discuss these results in relation to different risk factors, including some of those suggested by ADA [8] (Table 1).

OGTT in action

Age (years)	52.6 ± 14.2
BMI (kg/m ²)	28.5 ± 5.7
Waist Circumference (cm)	93.9 ± 14.2
FPG (mg/dl)	96.5 ± 12.1
Post-OGTT Plasma Glucose (mg/dl)	120.8 ± 41.9
Age ≥ 45 years (Y/N)	1534/592
Gender (M/F)	953/1173
Smoke (Y/N)	799/1327
Post-menopause (Y/N)	716/457
Family history of diabetes (Y/N)	588/1281
Family history of CV disease (Y/N)	161/1491
High Waist Circumference* (Y/N)	954/784
BMI kg/m ² ≥ 25 (Y/N)	1533/593
BMI kg/m ² ≥ 30 (Y/N)	717/1409
Metabolic Syndrome (Y/N)	805/1297
Hypertension (Y/N)	1580/546
HDL-cholesterol ≤ 35 mg/dl (Y/N)	161/1932
Triglycerides ≥ 250 mg/dl (Y/N)	161/1933

*

Table 1 shows the clinical data of our cohort. The majority of patients were females (n = 1173, 55.2%), 61.1% (n = 716) post-menopausal.

Out of the entire population, 799 (37.6%) were active smokers, 954 (54.9%) had a waist circumference ≥ 102 cm in males (≥ 88 in females), 1553 (70.1%) had a BMI ≥ 25 and 717 (33.8%) ≥ 30.

Essential hypertension was present in 74.3% (n = 1580), 31.5% (n = 588) had a family history of T2DM, 9.7% (n = 161) had a history of cardiovascular disease, 7.7% (n = 161) had HDL-cholesterol ≤ 35 mg/dl, 7.7% (n = 161) had TG ≥ 250 mg/dl, 72.1% (n = 1534) were older than 45 years and 38.3% (n = 805) fulfilled the diagnosis of Metabolic Syndrome (MS) in agreement to ATPIII criteria [17].

OGTT was compatible with normal glucose tolerance (NGT) only in half of our population (1123 subjects; 52.8%), while 472 subjects (22.2%) had isolated IFG, 167 (7.9%) isolated IGT, 241 (11.3%) combined IFG/IGT and 123 (5.8%) newly diagnosed T2DM. Interestingly, 34/123 T2DM patients (27.6%) had a FPG < 100 mg/dl.

OGTT in relation to the physical conditions, life style and family history

The alarming upsurge of T2DM in the world is accompanied by a similar rise in obesity and physical inactivity [1], therefore any intervention on lifestyle may bear positive effects not only on the course of diabetes, but also on its prevention [3-5,7] (Table 2).

Table 2 shows that OGTT was abnormal in 55.6% of subjects with a family history of T2DM, 63.4% of subjects with a history of previous cardiovascular events, 52.4% of subjects aged ≥ 45 years, 50.1% of post-menopausal women, 49.7% of smokers and in 57.7% of obese subjects (BMI ≥ 30). These same rate sequence in subjects without risk factors were 45.2%, 48.6%, 33.8%, 35.9%, 45.7% and 41.8% respectively.

A family history of diabetes is associated to an abnormal OGTT and reflects genetic susceptibility; however, although having a family history of T2DM is associated with better awareness of diabetes risk and participation to diabetes screening [18], the presence of a positive family history did not affect the result of lifestyle intervention in IGT subjects [19].

The strong relationship between abnormalities in glucose homeostasis and cardiovascular disease [20] is well known and, as

expected, in our population 63.4% of subjects with a positive history of cardiovascular events had an impaired OGTT. Surprisingly, on the other hand, even in absence of such a medical history, OGTT allows the diagnosis of prediabetes or T2DM in 48.6% of cases.

Aging and post-menopause are associated with worsening glucose homeostasis [15,21]. However, there are convincing data that the feared global pandemic of T2DM will not spare young people [22]. Data presented in this paper are eloquent: more than 35% of subjects younger than 45 and of pre-menopausal women have an abnormal OGTT.

Smoking is known to be associated with an increased risk of T2DM [23,24] and also to magnify its deleterious effect when combined with other risk factors [25]. However, in the US, smoking prevalence among people with T2DM and IFG has not changed and it is comparable to non-diabetic subjects [26]. Although tobacco control efforts should be intensified among population at high risk of complications and mortality, OGTT should be performed irrespective of smoking behaviour.

Risk factor		NGT (n, %)	preDM (n, %)	DM (n, %)
First-degree relative with DM	No (n = 1281)	702 (54.8)	514 (40.1)	65 (5.1)
	Yes (n = 588)	261 (44.4)	274 (46.6)	53 (9.0)
History of Cardiovascular disease	No (n = 1491)	766 (51.4)	636 (42.6)	89 (6.0)
	Yes (n = 161)	59 (36.6)	79 (49.1)	23 (14.3)
Age ≥ 45 years	No (n = 592)	392 (66.2)	184 (31.1)	16 (2.7)
	Yes (n = 1534)	731 (47.6)	696 (45.4)	107 (7.0)
Smokers	No (n = 1327)	721 (54.3)	533 (40.2)	73 (5.5)
	Yes (n = 799)	402 (50.3)	347 (43.4)	50 (6.3)
Post-menopausal condition	No (n = 457)	293 (64.1)	147 (32.2)	17 (3.7)
	Yes (716)	357 (49.9)	314 (43.8)	45 (6.3)
BMI	< 25 (n = 593)	402 (67.8)	167 (28.1)	24 (4.1)
	25-29.9 (n = 816)	418 (51.2)	347 (42.6)	51 (6.2)
	≥ 30 (n = 717)	303 (42.3)	366 (51.0)	48 (6.7)
Hypertension	No (n = 546)	360 (65.9)	165 (30.2)	21 (3.9)
	Yes (n = 1580)	763 (48.3)	715 (45.2)	102 (6.5)
Metabolic Syndrome	No (n = 1297)	902 (69.5)	349 (27.0)	46 (3.5)
	Yes (n = 805)	210 (26.1)	518 (64.3)	77 (9.6)
HDL ≤ 35 mg/dl	No (n = 1932)	1029 (53.3)	794 (41.1)	109 (5.6)
	Yes (n = 161)	76 (47.2)	71 (44.1)	14 (8.7)
TG ≥ 250 mg/dl	No (n = 1933)	1043 (53.9)	779 (40.4)	111 (5.7)
	Yes (n = 161)	62 (38.5)	87 (54.1)	12 (7.4)

Finally, if it is true that in obesity there is a higher prevalence of glucose abnormalities, it is not uncommon to find these alterations in subjects with normal BMI.

As shown in Table 2, though the prevalence of prediabetes and T2DM was very high in obese subjects (BMI ≥ 30) and in case of overweight (25 < BMI < 30), it still remained at a remarkable level in subjects with normal BMI (respectively 28.1% and 4.1%).

The adoption of lifestyle changes is mandatory and essential also in subjects with normal BMI and impaired OGTT.

OGTT in hypertension

Alterations of glucose metabolism are common in hypertension [27]. As shown in the (Table 2), over 50% of hypertensives had an abnormal OGTT. Of these, 12.5%, corresponding to 6.5% of all hypertensives, received a new diagnosis of T2DM. As the coexistence of hypertension and T2DM is harmful [28], it should be investigated in order to take appropriate therapeutic measures. A tight control of blood pressure in patients with T2DM may achieve important reductions in diabetes-related morbidity and mortality and weight reduction lowers blood pressure while improving blood glucose and lipid levels [29,30].

The finding of a high prevalence of prediabetes in hypertension (45.2%) is indisputable and should therefore be systematically sought by OGTT. The detection of prediabetes in hypertensives is crucial to develop strategies for cardiovascular protection intended to diminish the consequences of an accelerated development of diabetes, together with its cardiovascular and renal deleterious effects [31], through intensive lifestyle management and pharmacologic therapies [32].

Anyway, even in the absence of hypertension, OGTT demonstrates its ability to detect a fair proportion of subjects with prediabetes (30.2%) and T2DM (3.9%).

OGTT in MS and atherogenic dyslipidemia

The prevalence and severity of MS are rising dramatically [17,33]. It is easy detection using ATPIII criteria [17] is a simple tool to stratify cardiovascular risk. FPG is one of the five criteria used by ATPIII and recently its cut-off value was lowered from 110 to 100 mg/dl [17] in agreement with ADA criteria for the diagnosis and classification of T2DM [9,15].

Though this cut-off change was introduced aiming to include in MS definition the majority of subjects with abnormal glucose metabolism, authoritative studies have established that IFG adds very few to IGT in predicting incident T2DM [34].

As shown in Table 2, 73.9% of patients with MS had an impaired OGTT; of these, 12.9% fulfilled the diagnostic criteria of T2DM. In turn, T2DM patients with MS bear a cardiovascular risk significantly higher than NGT subjects, also when affected by MS [34]. Thus, the attention to MS is important, but it may not be sufficient, since an abnormal OGTT is an independent cardiovascular risk factor.

Table 2 also shows the performance of OGTT in relation to the presence or absence of two additional risk factors for T2DM listed by ADA [8]: a TG level \geq 250 mg/dl and HDL-cholesterol \leq 35 mg/dl. These are part of the classification criteria for MS though, in this case, their threshold values are more stringent [17].

High TG levels coupled to low HDL levels characterize the atherogenic dyslipidemia, a phenotype associated with increased cardiovascular risk [35].

As evident in Table 2, OGTT was abnormal in 61.5% of subjects with TG \geq 250 mg/dl and in 52.8% of subject with HDL-cholesterol \leq 35 mg/dl. In the absence of those risk factors, these percentages become 46.1% and 46.7%, respectively. Even in this context, regardless of the risk factors considered, the OGTT confirms its usefulness in screening for T2DM and cardiovascular risk.

Conclusion

The OGTT, developed to determine the ability of an individual to maintain glucose homeostasis, can be considered a screening test not only for abnormal glucose metabolism, but also for cardiovascular risk stratification. Although dated, the OGTT may constitute a viable option to deal with the expected pandemic of T2DM.

In this review, the data shown are consistent with the concept that, wherever used, the OGTT is unerringly able to detect a substantial proportion of cardio metabolic risk that would otherwise be unrecognised.

In fact, the absence of the risk factors suggested by ADA is unable to rule out an alteration of glucose homeostasis; regardless of any risk

factor considered, OGTT appears consistently able to identify a substantial proportion, at least 30%, of subjects with impaired glucose metabolism that, if untreated, would encounter serious health problems, progressing to overt T2DM and developing micro and macrovascular complications. Furthermore, prediabetes is burdened, per se, by an increased risk of diabetic retinopathy [3,36] cardiovascular events [37] and sudden death [38].

It is obvious that the earlier the recognition will take place, the better the prevention will be. Recently, the benefits of a dietary intervention in subjects with newly diagnosed T2DM have been reported in patients with a mean FPG of 162 ± 34 mg/dl, indicating a delayed diagnosis [7]. An earlier detection would have yielded benefits far superior to those obtained with delayed treatment.

Furthermore, it is worth noting that, in our present study, all subjects with newly diagnosed T2DM had a FPG $<$ 126 mg/dl.

Therefore, we believe that our evidence demonstrates that OGTT should never be neglected and, as a matter of fact, its execution should be advocated as a screening test in asymptomatic populations to search for prediabetes before diabetes.

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