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Original Article

Impaired glucose metabolism in hypertensive patients with/without the metabolic syndrome

Gian Piero Carnevale Schianca [a], Gian Paolo Fra [a,*], Mara Steffanini [a,b], Gabriele Pogliani [a,b], Cecilia Marconi [a,b], Marcello Bigliocca [a,b], Mario Pirisi [a,b]

[a] Internal Medicine, Azienda Ospedaliera Universitaria "Maggiore della Carità", Novara, Italy
[b] Department of Translational Medicine, Università del Piemonte Orientale "A. Avogadro", Novara, Italy

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ABSTRACT

Background: In hypertension clinics, screening patients for the metabolic syndrome (MetS) is common practice, while performing the cumbersome oral glucose tolerance test (OGTT) is not. How large is the underestimation of diabetes and prediabetes that ensues is unknown.
Methods: We recruited N = 1397 patients with essential arterial hypertension who underwent a 75-g OGTT and were classified as normally glucotolerant (NGT) or having impaired glucose metabolism (IGM), and as affected or not by MetS (ATPIII criteria). The agreement between the OGTT and the ATPIII criteria in attributing a high cardiovascular risk was estimated by matching the categories of MetS and no-MetS with NGT and IGM.
Results: n = 677/1397 patients (48%) satisfied criteria for MetS, while n = 757/1397 (54%) had an IGM. MetS and IGM were both present in n = 512/1397 patients (36.6%), and both absent in n = 475/1397 (34%). Further n = 410/1397 patients (29%) were discordant for the two conditions: n = 165/410 (40%) had the MetS but were NGT, and n = 245/410 (60%) had IGM but no MetS. Among IGM patients, n = 168/757 (22%; of which 45 had no MetS) received a new diagnosis of diabetes based on OGTT criteria. Among all discordant patients, those with IGM and no MetS were more commonly males ($p < 0.001$), and had older age ($p < 0.001$) and lower body mass index ($p < 0.05$).
Conclusions: Among patients with hypertension, the estimate of the prevalence of diabetes and prediabetes, hence of the global cardiovascular risk, can be seriously flawed unless an OGTT is performed. Our results support a wider use of the OGTT in the management of hypertension.

1. Introduction

The pharmacological management of hypertension should be graded as a function of global cardiovascular (CV) risk, to which, as outlined in the 2007 guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [1], both the metabolic syndrome (MetS) and type 2 diabetes contribute strongly. Indeed, fasting plasma glucose (FPG) had been incorporated in all sets of MetS-defining criteria proposed from 2001 [2].

In 2004 the American Heart Association/National Heart, Lung, and Blood Institute lowered the threshold for FPG from 110 to 100 mg/dl [3], a value coincident with that chosen by the American Diabetes Association (ADA) to qualify for impaired fasting glucose (IFG) [4]. Clearly, the rationale behind this decision was the attempt to gather under the label MetS – the component criteria of which are strictly linked to insulin resistance [3,4] – most subjects with an altered glucose homeostasis, not only diabetics. However, it has been shown that an altered glucose homeostasis may be missed if an oral glucose tolerance test (OGTT) is not performed [5]. In fact, when FPG is used alone as a screening tool, an appreciable number of diabetic subjects are not diagnosed [5,6]. Moreover, to recognize an impaired glucose tolerance (IGT) an OGTT is by definition required. Similarly to patients with MetS [7], IGT patients are at high risk not only for type 2 diabetes, but also for CV events [8,9]: taking into consideration this information, the ESH/ESC guidelines include among CV risk factors to be ascertained both a FPG ≥ 100 mg/dl and an abnormal OGTT [1]. In recent years, however, OGTT has fallen out of favor in clinical practice in general, and in the risk assessment of hypertensive patients in particular [10–12]. Whether omitting OGTT has a negligible impact on the correct CV risk stratification, being CV risk thoroughly defined by the widened definition of IFG, is unknown. To clarify this issue, we reviewed data from a large group of patients attending an hypertension clinic, who systematically underwent an OGTT, looking for possible discrepancies in the CV risk stratification of these patients when OGTT data were omitted.

* Corresponding author at: Internal Medicine, Azienda Ospedaliera Universitaria "Maggiore della Carità", C.so Mazzini 18, 28100 Novara, Italy. Tel.: +39 0321 3733273; fax: +39 0321 3733361.
E-mail address: g.fra@mclink.it (G.P. Fra).

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2. Methods

2.1. Patients

The study population originated from the data base of patients attending the Hypertension Clinic of an Academic Hospital from January 1, 2000, to December 31, 2012. Having excluded subjects with known type 2 diabetes, those affected by endocrine, liver and/or renal disease, and those taking medications affecting glucose or insulin metabolism, we recruited 1397 subjects with essential arterial hypertension. After at least 5 days of a weight-maintaining diet (55% of calories from carbohydrates, 25% from fats, 20% from proteins) and avoidance of strenuous exercise, all these patients, otherwise considered healthy on the basis of physical examination and routine laboratory exams, had undergone per protocol a standard 75-g OGTT. On the same day, patients had their body mass index (BMI) calculated in kg/m^2, and their waist circumference (WC) measured in cm midway between the lowest rib and the iliac crest while standing.

2.2. Bio-humoral methods

All patients underwent a standard 75-g OGTT, during which venous blood samples were drawn at baseline and 2 hours later for determination of FPG and 2-h plasma glucose (2hPG) using the glucose oxidase method. Moreover, measurement of total (CT) and HDL-cholesterol (HDL), using enzymatic procedures, and of triglycerides (TG) using a colorimetric assay, was obtained in all cases. All these assays were performed by a central laboratory with an ADVIA 1650/2400 Chemistry System.

2.3. Definitions of Metabolic Syndrome and Altered Glucose Metabolism

According to the 2009 Joint Scientific Statement [13], MetS was defined by five criteria: WC ≥ 102 cm (88 for women), TG ≥ 150 mg/dl, blood pressure ≥ 130/85 mmHg (or treatment for hypertension), HDL < 40 mg/dl (50 for women) and FPG ≥ 100 mg/dl. Hypertensive subjects were classified as having the MetS if they fulfilled two or more of the aforementioned criteria, in addition to hypertension. According to the ADA criteria and the results of the OGTT [4], a subject was classified as having normal glucose tolerance (NGT) when FPG < 100 mg/dl and 2hPG < 140 mg/dl, type 2 diabetes when FPG > 125 and/or 2hPG ≥200 mg/dl, isolated impaired fasting glucose (IFG) when FPG 100-125 mg/dl and 2hPG < 140 mg/dl, isolated impaired glucose tolerance (IGT) when FPG < 100 mg/dl and 2hPG 140-199 mg/dl, and a combination of IFG and IGT (IFG/IGT) when FPG 100-125 mg/dl and 2hPG 140-199 mg/dl. For the purposes of the study, hypertensive subjects with IFG, IGT, IFG/IGT or diabetes were lumped into a single group, called impaired glucose metabolism (IGM).

2.4. Statistical analysis

Medians and 95% confidence interval of the medians were the measures of central tendency and dispersion used throughout the paper to summarize data with continuous distribution. A 2 × 2 table was constructed, in which the categories of MetS and absence of MetS (ATPIII criteria) were matched with the categories of NGT and IGM (OGTT criteria). The categorical variables were described both by the number of cases and by the proportion of participants falling into each category. The agreement between the OGTT and the ATPIII criteria in attributing an high CV risk to hypertensive patients was estimated by calculating the Cohen's κ coefficient and performing the McNemar χ^2 test. The associations between categorical variables and the comparisons of continuous variables between groups were analyzed using the χ^2 test and the Mann-Whitney test, respectively. The level chosen to indicate statistical significance was <0.05 (two-tails) for all statistical tests. The statistical software package StatSoft 5.1 STATISTICA Inc. (2300 East 14th Street, TULSA, OK 74104, USA) was used for statistical analysis.

3. Results

Table 1 shows the clinical features of the 1397 hypertensive subjects enrolled in the study. The data are presented for the entire study population as well as for either gender.

Five hundred thirty-nine patients (38.6%) were smokers (≤10 cigarettes/day) and 499 of the 744 women (67.1%) were post-menopausal. A BMI ≥ 30 kg/m^2 (indicating obesity) was observed in 534 (38.2%).

We identified 677 cases satisfying ATPIII criteria forMetS (48.5%), while criteria for NGT, IFG, IGT, IFG/IGT and type 2 diabetes were fulfilled in 640 (45.8%), 304 (21.7%), 108 (7.7%), 177 (12.7%) and 168 cases (12.1%), respectively. Therefore, the majority of hypertensive patients tested by OGTT (n = 757; 54.2%) had an IGM.

In Table 2, the categories of MetS and absence of MetS have been matched to the categories of NGT and IGM. For each of the four categories, the number of cases and the percentages are presented. Approximately one third of hypertensive subjects (n = 512, 36.6%) had both MetS and IGM, and another one third (n = 475, 34%) had NGT and no MetS.

Analyzing in further detail the groups of hypertensive patients with IGM (n = 757) and with MetS (n = 677), we observed that 32.4% of the former group (n = 245) did not have MetS, while 24.4% of the latter group (n = 165) were NGT.

The agreement between the ATPIII criteria and the OGTT in attributing an high CV risk to hypertensive patients was moderate (κ = 0.4). We rejected the null hypothesis that the proportion of patients with the outcome of interest (high cardiovascular risk) identified by the two tests (ATPIII criteria and OGTT) was similar, since the OGTT identified a significant percentage of hypertensive patients (17.6%, n = 245) who, despite not having the MetS, had actually a high cardiovascular risk being affected by IGM, compared to the percentage of hypertensive

Table 1
Characteristics of the 1397 hypertensive patients studied.

	Hypertensive patients (n = 1397)	Males hypertensive patients (n = 653)	Females hypertensive patients (n = 744)
Age years	55 (54–56)	53 (52–54.1)	57 (55–59)
BMI kg/m^2	28.4 (28.1–28.7)	28.4 (28.1–28.7)	28.5 (27.9–29.3)
WC cm	97 (96–97.5)	99 (98–100)	94 (92–95)
FPG mg/dl	98 (97–99)	99 (98–100)	97 (96–98)
2hPG mg/dl	117 (115–120)	113 (110–117)	121 (117–125)
Total cholesterol mg/dl	216 (214–219)	209 (206–213)	221 (217–224.7)
Triglycerides mg/dl	120 (115.4–123)	123 (118–128)	116 (109.2–122)
HDL-cholesterol mg/dl	50 (49–51)	45 (44–46)	54 (53–55.7)

Footnote: Continuous variables are presented as median and (95% CI of median).