


## RESEARCH ARTICLE

# Insulin resistance and beta-cell dysfunction in newly diagnosed type 2 diabetes: Expression, aggregation and predominance. *Verona Newly Diagnosed Type 2 Diabetes Study 10*

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## Funding information

Italian Ministry of the Education, University and Research, Grant/Award Numbers: PRIN 2009WYP4AS, PRIN 2015373Z39\_002, PRIN 2015373Z39\_004, PRIN 2010098WFZ2\_003  
Open Access Funding provided by Università degli Studi di Verona within the CRUI-CARE Agreement.

## Abstract

**Aims:** We investigated quantitative expression, mutual aggregation and relation with hyperglycemia of insulin resistance (IR) and beta-cell dysfunction (BCD) in newly diagnosed type 2 diabetes.

**Methods:** We assessed IR with euglycemic hyperinsulinemic clamp and BCD with modelled glucose/C-peptide response to oral glucose in 729 mostly drug-naïve patients. We measured glycated hemoglobin, pre-prandial, post-prandial and meal-related excursion of blood glucose.

**Results:** IR was found in 87.8% [95% confidence intervals 85.4–90.2] and BCD in 90.0% [87.8–92.2] of subjects, ranging from mild to moderate or severe. Approximately 20% of subjects had solely one defect: BCD 10.8% [8.6–13.1] or IR 8.6% [6.6–10.7]. Insulin resistance and BCD aggregated in most subjects (79.1% [76.2–82.1]). We arbitrarily set nine possible combinations of mild, moderate or severe IR and mild, moderate or severe BCD, finding that each had a similar frequency (~10%). In multiple regression analyses parameters of glucose control were related more strongly with BCD than with IR.

**Conclusions:** In newly-diagnosed type 2 diabetes, IR and BCD are very common with a wide range of expression but no specific pattern of aggregation. Beta-cell dysfunction is likely to play a greater quantitative role than IR in causing/sustaining hyperglycemia in newly-diagnosed type 2 diabetes.

## KEYWORDS

beta-cell dysfunction, hyperglycemia, insulin resistance, newly diagnosed, type 2 diabetes mellitus

Enzo Bonora and Maddalena Trombetta equally contributed to this work

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## 1 | INTRODUCTION

Type 2 diabetes is a heterogeneous disorder with hyperglycemia as the common hallmark of several different clinical phenotypes. Within the octet of abnormalities contributing to hyperglycemia,<sup>1</sup> beta-cell dysfunction (BCD) and insulin resistance (IR) are dominant. The two defects are thought to be variably associated and it is a well-established clinical concept (a sort of dogma) that in a subtype of patients BCD, and in another IR, predominates.<sup>2</sup> However, the prevalence of these extreme conditions and intermediate conditions is poorly known. Furthermore, the proportions of type 2 diabetes patients without IR and/or without BCD, if any, are unknown. Finally, it is still uncertain whether one defect clearly predominates in dictating hyperglycemia. Addressing these clinically relevant questions requires deep phenotyping of large numbers of patients and also of healthy controls to derive reference intervals for insulin sensitivity and beta cell function.

In the present study we assessed BCD and IR with state-of-the-art techniques in a large cohort of mostly drug-naïve newly diagnosed type 2 diabetes patients, thereby avoiding the potential confounding effect of glucose lowering drugs and longstanding hyperglycemia (glucose toxicity). We related these two pathophysiological features to several glycaemic parameters. Aims were to better understand how variably expressed are these defects at time of diagnosis, how they aggregate in the single individual and which of the two is more closely associated with hyperglycemia.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

We examined newly diagnosed type 2 patients from the Verona Newly Diagnosed Type 2 Diabetes Study, an ongoing study on genetics, pathophysiology and clinical features/outcomes of patients with newly diagnosed type 2 diabetes.<sup>3–10</sup> The protocol was approved by the local Ethics Committee and is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (n. NCT01526720). As of 1 January 2002, all type 2 diabetic patients referred to the Diabetes Clinic embedded into the Division of Endocrinology, Diabetes and Metabolic Diseases of the University and Hospital Trust of Verona and whose disease was diagnosed in the previous 6 months were offered to participate in this study. Recruitment was ended on 31 December 2015 and a follow-up was then planned and is ongoing. All participants gave an informed written consent. The clinical evidence on which the diagnosis of type 2 diabetes had been made was reviewed at the recruitment and the diagnosis was confirmed according to standard criteria.<sup>11</sup> The large majority of patients were drug-naïve (~95%) or, if already treated with antidiabetic drugs (~5%), underwent a treatment washout of at least 1 week before metabolic tests were performed. Exclusion criteria were age >75 years, non-Italian ancestry, current insulin treatment, presence of anti-glutamic acid decarboxylase (GAD) antibodies, clinical suspect of Maturity Onset Diabetes

of the Young (MODY), pancreatogenic or other varieties of secondary (or type 3) diabetes, history of malignancies or any condition severely impairing liver and/or kidney function. Here we report data collected from the 729 patients who had both BCD and IR data available. A subgroup of 566 subjects also performed multiple home blood glucose monitoring (HBGM) with a glucose metre.

### 2.2 | Clinical data

Weight and height were measured and body mass index (BMI) calculated by dividing weight in kilograms by the square of height in metres. Waist circumference was measured by a tape metre at the level of the umbilicus. Blood pressure was measured at the right arm when sitting. Venous blood was drawn in the morning after an overnight fast. Plasma glucose (PG) was measured by a glucose oxidase method and glycated hemoglobin (HbA1c) with a high performance liquid chromatography method, standardized according to International Federation of Clinical Chemistry. In case of discrepancy between the 3 tests (fasting PG, 2-h PG, HbA1c) the one documenting diabetes (value above the diagnostic cut-off) was used for diagnosis according to standard criteria.<sup>11</sup> Serum lipids and creatinine were measured with standard methods.

### 2.3 | Home blood glucose monitoring

A subgroup of 566 subjects accepted to receive a glucose metre (Menarini Diagnostics, Florence, Italy) and to assess capillary blood glucose (BG) before and 2 h after breakfast, lunch and dinner on 5 days within 2 weeks. Mean pre-prandial and post-prandial BG at breakfast, lunch and dinner and glucose excursion after each meal were calculated. The mean pre-meal and post-meal and the mean excursion after meal were then calculated.

### 2.4 | Metabolic studies

Metabolic studies (euglycemic hyperinsulinemic clamp and oral glucose tolerance test (OGTT) with mathematical modelling of beta-cell function) were carried out on two separate days in random order. On both days, patients were admitted to the Metabolic Clinic Research Centre at 07:30 after an overnight fast. Studies were carried out in a quiet, temperature controlled (22°C) room. On both occasions, all blood samples were collected in pre-chilled tubes and readily spun at 1500 g. Plasma and serum specimens were stored at –80°C.

### 2.5 | Euglycemic hyperinsulinemic clamp

The euglycemic hyperinsulinemic clamp (briefly insulin clamp) was performed to assess insulin sensitivity as described by DeFronzo et al.<sup>12</sup>

During the entire test the patient was lying in bed. One teflon catheter was introduced into an antecubital vein for the infusion of test substances. Another teflon catheter was placed retrogradely into a wrist vein for sampling arterialised venous blood, according to the "hot box" technique. Baseline blood samples were collected and a standard insulin clamp was initiated (intravenous prime:  $4.8 \text{ nmol m}^{-2}$  Body Surface Area [BSA]; continuous infusion:  $240 \text{ pmol min}^{-1} \text{ m}^{-2}$  BSA). Plasma glucose was allowed to decline until it reached  $5.5 \text{ mmol/L}$ , after which glucose clamping started with a glucose concentration goal of  $5 \text{ mmol/L}$ . The duration of the insulin clamp was at least  $120 \text{ min}$ , but it was prolonged in some subjects by  $15\text{--}60 \text{ min}$ , if and as needed, to ensure at least  $60 \text{ min}$  of insulin clamp at euglycemia. Timed blood samples were collected to measure hormone and substrate levels.

## 2.6 | Oral glucose tolerance test

The OGTT ( $75 \text{ g}$ ) was performed to assess beta cell function. During the entire test patients were sitting in a comfortable cardiac chair. One teflon ( $21 \text{ g}$ ) venous catheter was inserted into an antecubital vein for blood sampling and kept patent with heparinised normal saline solution. After a  $30\text{-min}$  rest to establish a baseline condition, subjects ingested  $75 \text{ g}$  of glucose in  $300 \text{ ml}$  of water over  $5 \text{ min}$ . Blood samples to measure glucose, C-peptide and insulin concentrations were collected at times  $-10, 0, +15, +30, +45, +60, +90, +120, +150, +180, +210$  and  $+240 \text{ min}$ . In some patient further blood samples were collected at  $+270'$  and  $+300'$ . Urines were collected to measure glycosuria.

## 2.7 | Mathematical modelling of beta cell function

The analysis of the glucose and C-peptide curves during the OGTT follows the general strategy described in previous publications<sup>13–15</sup> with some modifications, and builds upon previous works from other laboratories.<sup>16–18</sup> The kinetics of C-peptide is described with a two-compartment model, in which the two pools (1 and 2) exchange with each other and the irreversible loss of the hormone is from pool 1, the same where C-peptide concentration is measured. C-peptide kinetic parameters are computed according to the equations by Van Cauter et al.<sup>19</sup>

Herein are the equations describing the model of glucose-induced insulin secretion during an OGTT:

$$dcp_1(t)/dt = \text{ISR}(t) + cp_2 \cdot k_{12} - (k_{01} + k_{21}) \cdot cp_1 \quad (1)$$

where  $\text{ISR}$  = insulin secretion rate,  $cp_1$  = C-peptide mass in the sampling (accessible) compartment,  $cp_2$  = C-peptide mass in the remote compartment,  $k_{12}$  and  $k_{21}$  = rate constants of the exchange between the two C-peptide compartments, and  $k_{01}$  = rate constant of the irreversible loss of C-peptide from the accessible compartment. Note that the values of the volume of distribution of C-peptide pool 1 (accessible compartment),  $k_{12}$ ,

$k_{21}$ , and  $k_{01}$  are computed according to the equations by Van Cauter et al.<sup>19</sup>

$$\text{ISR}(t) = \text{BSR} + \text{DSR}(t) + \text{PSR}(t) \quad (2)$$

where  $\text{BSR}$  = basal insulin secretion rate ( $\text{ISR}$ ), derivative secretion rate ( $\text{DSR}$ ) =  $\text{ISR}$  due to the derivative (or dynamic) component, and proportional secretion rate ( $\text{PSR}$ ) =  $\text{ISR}$  due to the proportional (or static) component.

$$\text{BSR} = \text{CP}_{ss} \cdot V_1 \cdot k_{01} \quad (3)$$

where  $\text{CP}_{ss}$  is basal C-peptide concentration and  $V_1$  is the volume of the accessible compartment of C-peptide.

From the modelling viewpoint,  $\text{DSR}(t)$  and  $\text{PSR}(t)$  are the components which in intravenous glucose tolerance tests or hyperglycaemic clamps describe classical first phase insulin secretion and second phase insulin secretion, respectively. Furthermore, from a physiological viewpoint, the sum of basal insulin secretion rate and  $\text{PSR}(t)$  describes the relationship linking glucose concentration and  $\text{ISR}$ , in the absence of the derivative component ( $\text{DSR}$ ).

$\text{DSR}(t)$  and  $\text{PSR}(t)$  are mathematically defined as follows:

$$\text{DSR}(t) = X1(t) \cdot \tau^{-1} \quad (4)$$

$$dX1(t) / dt = s1 \cdot [dG(t)/dt] / [\log(1.1 + t)] - X1(t) \cdot \tau^{-1} \text{ if } dG(t)/dt > 0 \quad (5)$$

$$dX1(t) / dt = -X1(t) \cdot \tau^{-1} \text{ if } dG(t)/dt \leq 0 \quad (6)$$

where  $s1$  = glucose sensitivity of derivative control ( $\text{DC}$ ) of insulin secretion,  $G$  =  $\text{PG}$  concentration,  $X1$  = C-peptide (insulin) mass made available for the derivative component of insulin secretion,  $\tau$  = time constant of the derivative component of insulin secretion, and the term  $\log(1.1 + t)$  accommodates the time-associated decline of  $s1$  documented in humans during a hyperglycaemic stimulus.<sup>20</sup>

$$\text{PSR}(t) = X2(t) \cdot \delta^{-1} \quad (7)$$

$$dX2(t) / dt = \sigma 2 \cdot [G(t) - \theta] - X2(t) \cdot \delta^{-1} \quad (8)$$

where  $\sigma 2$  = glucose sensitivity of the proportional component of insulin secretion,  $X2$  = C-peptide (insulin) mass made available for the proportional component of insulin secretion,  $\delta$  = time constant of the proportional component of insulin secretion,  $\theta$  = glucose threshold above which the beta-cell responds with the proportional component of insulin secretion to  $\text{PG}$  concentration.

This model was implemented in the SAAM 1.2 software (SAAM Institute, Seattle, WA)<sup>21</sup> to estimate its unknown parameters. Numerical values of the unknown parameters were estimated by using nonlinear least squares. Weights were chosen optimally, that is, equal to the inverse of the variance of the measurement errors, which were assumed to be additive, uncorrelated, with zero mean, and a coefficient of variation of  $6\text{--}8\%$ . The unknown parameters of the model are:  $\text{CP}_{ss}$ ,  $\sigma 1$ ,  $\tau$ ,  $\sigma 2$ ,  $\delta$ , and  $\theta$ .

The main physiological outputs of the model we used in this study were:

*Derivative control* (DC units:  $(\text{pmol}\cdot\text{m}^{-2}\text{ BSA})/(\text{mmol}\cdot\text{l}^{-1}\cdot\text{min}^{-1})$ ): it is the amount of insulin secreted in response to a rate of glucose increase of 1 mmol/L per min which lasts for 1 min.

*Proportional control* (PC units:  $(\text{pmol}\cdot\text{min}^{-1}\cdot\text{m}^{-2}\text{ BSA})/(\text{mmol}\cdot\text{l}^{-1})$ ): it is the glucose sensitivity of the proportional component (stimulus-response curve) of insulin secretion.

These two main components of insulin secretion (DC and PC) were previously described by others and ourselves<sup>13–17</sup> and are described also in a classic textbook of Endocrinology.<sup>18</sup> During a hyperglycaemic clamp, DC accounts for first phase, PC for second phase insulin secretion.<sup>15,18</sup>

## 2.8 | Definition of beta-cell dysfunction and insulin resistance

Cut off values for BCD were set at 25th percentile of DC or PC observed in 340 subjects with normal glucose regulation recruited within the GENFIEV study.<sup>22</sup> In particular cut-off values of DC and PC were 900  $(\text{pmol}\cdot\text{m}^{-2}\text{ BSA})/(\text{mmol}\cdot\text{l}^{-1}\cdot\text{min}^{-1})$  and 98  $(\text{pmol}\cdot\text{min}^{-1}\cdot\text{m}^{-2}\text{ BSA})/(\text{mmol}\cdot\text{l}^{-1})$  respectively.

Cut-off value defining IR was set at 25th percentile of *M* values observed during euglycemic hyperinsulinemic clamp in 386 subjects with normal glucose regulation recruited within the GISIR study.<sup>23</sup> In particular, it was 1100  $\mu\text{mol}\cdot\text{min}^{-1}\cdot\text{m}^{-2}\text{ BSA}$ . This cut-off is similar to the cut-off value of bottom quartile of *M* values observed in 1146 subjects with normal glucose tolerance from the EGIR database.<sup>24</sup>

## 2.9 | Statistics

Data are presented as median and interquartile range [IQR] or as percentage of total with 95% confidence intervals (CI). Statistical analyses (chi square test, Kruskal Wallis test, Pearson's correlation, multiple regression analysis) were performed with standard techniques. Logarithmic transformation was applied when appropriate. Average of 5 days of HBGM with 6 readings per day were used for assessing pre-prandial and post-prandial BG and meal glucose excursions. In multivariable analyses, in which glucose parameters were dependent variables, age, sex, *M*-clamp and DC and/or PC of insulin secretion were included as independent variables. Additional models included also BMI or waist circumference.

## 3 | RESULTS

Median age was 60 years [IQR 52–66], males were 69% of the sample. Median fasting PG, HbA1c and BMI were 7.0 mmol/L [6.2–7.9], 49 mmol/mol [43–56], 6.6% [6.0–7.3], and 29.3 kg/m<sup>2</sup> [26.5–32.7], respectively. Median pre-prandial glucose was 6.1 mmol/L [5.5–7.1] and median post-prandial glucose was 7.4 mmol/L [6.5–8.8]. Median

DC and PC values were 444 [52–958] and 47 [25–76]  $(\text{pmol}\cdot\text{m}^{-2}\text{ BSA})/(\text{mmol}\cdot\text{l}^{-1}\cdot\text{min}^{-1})$ , respectively. Median *M*-clamp was 604 [380–865]. Other clinical features of subjects under study are reported in Table 1.

As many as 87.8% [95% CI 85.4–90.2] and 90.0% [87.8–92.2] of subjects had IR and BCD (a DC and/or a PC deficit), respectively, whereas 79.1% [76.2–82.1] had both defects. Ten subjects, 1.4% [0.05–2.2] of the sample, displayed normal values of *M*-clamp, DC and PC. However, nine out of them had an *M*-clamp value and/or a PC value barely above threshold. These subjects had very mild hyperglycemia. Table 1 reports the main clinical features of subjects with isolated BCD, isolated IR or both conditions. Subjects with isolated BCD had lower BMI and triglycerides and higher density lipoprotein cholesterol. Subjects with combined defects had higher HbA1c and glucose levels. Supplementary Tables 1 and 2 reports these data in men and women, separately.

*M*-clamp, but not DC nor PC, was inversely correlated with BMI ( $r = -0.430$ ,  $p < 0.001$ ) and waist circumference ( $r = -0.447$ ,  $p < 0.001$ ).

As shown in Figure 1, slightly less than 9% had isolated IR (8.6% [6.6–10.7]), and slightly less than 11% had an isolated BCD without IR (10.8% [8.6–13.1]). In case of isolated BCD, the combination of DC and PC defects was definitely more common (8%) than the very rare isolated DC (<1%) or the isolated PC (2%). A fraction of subjects with IR had a defect of PC without a defect of DC (~15%) or, alternatively, had a defect of DC without a defect of PC (~5%).

Abnormal PC and *M*-clamp values ranged within one order of magnitude, with several subjects having a 5–10 times greater defect than others (Figure 2). *M*-clamp values were not significantly different across the 10 deciles of PC, and PC values were similar across the 10 deciles of *M*-clamp (supplementary table 3).

In the whole sample no correlation was found between *M*-clamp and DC values ( $r = -0.011$ ,  $p =$  not significant [NS]). A weak, albeit significant, positive correlation was found between *M*-clamp and PC values ( $r = 0.116$ ,  $p = 0.002$ ). Derivative control and PC values were significantly correlated ( $r = 0.327$ ,  $p < 0.001$ ).

We stratified subjects with BCD and/or IR into tertiles of insulin sensitivity, of DC and of PC of insulin secretion. Then, we examined the frequency of the nine possible metabolic combinations as defined by the association of mild (+), moderate (++) , severe (+++) IR with mild (+), moderate (++) , severe (+++) BCD (defect in DC or, alternatively, in PC). Figure 3 shows that subjects under study were distributed rather uniformly across these metabolic combinations and this was true for IR and DC defect as well as for IR and PC defect.

We ran multivariable regression analyses with parameters of glucose control as dependent variables and DC, PC and *M*-clamp as independent variables in models including also age and sex (Table 2). In these analyses, the beta coefficients of insulin sensitivity (*M*-clamp) and insulin secretion (DC or PC) were significantly associated with all parameters describing glucose control. Interestingly, the beta coefficients of PC were two to three fold higher and those of DC were generally lower than those of *M*-clamp across all models. Results were similar when we stratified subjects according to sex, when both DC and PC were included in the same model or when also BMI

TABLE 1 Main clinical features of subjects under study

Variable	All (n = 729)	No defect (n = 10)	Isolated BCD (n = 79)	Isolated IR (n = 63)	Combined defect (n = 577)	p Value
Sex (male, %)	69	80	76	40	71	<0.001
Age (years)	60 [52–66]	59 [46–66]	61 [52–66]	59 [51–66]	59 [52–66]	NS
Body mass index (Kg/m <sup>2</sup> )	29.3 [26.5–32.7]	24.9 [23.0–28.1]	26.2 [24.3–27.9]	30.5 [28.0–34.7]	29.6 [27.0–32.9]	<0.001
Smoking (past/current, %)	50.5	33.3	59.5	37.7	50.9	0.054
HbA1c (mmol/mol)	49 [43–56]	40 [37–45]	48 [42–54]	44 [41–50]	50 [44–58]	<0.001
Fasting PG (mmol/L)	7.0 [6.2–7.9]	5.7 [5.2–6.2]	6.7 [5.9–7.3]	6.4 [5.5–7.1]	7.2 [6.4–8.3]	<0.001
2 h OGTT PG (mmol/L)	12.9 [10.4–16.0]	7.3 [5.4–9.8]	11.3 [8.7–13.8]	10.1 [8.2–11.5]	13.7 [11.1–16.4]	<0.001
Pre-prandial BG (mmol/L)	6.1 [5.5–7.1]	5.3 [4.9–5.7]	5.7 [5.2–6.4]	5.8 [5.2–6.4]	6.2 [5.7–7.3]	<0.001
Post-prandial BG (mmol/L)	7.4 [6.5–8.8]	5.9 [5.3–6.1]	6.7 [6.2–7.6]	6.8 [6.0–7.4]	7.6 [6.7–9.1]	<0.001
Prandial BG increase (mmol/L)	1.28 [0.7–2.2]	0.15 [–0.002–0.99]	1.14 [0.7–1.7]	0.92 [0.5–1.5]	1.39 [0.7–2.3]	<0.001
LDL cholesterol (mmol/L)	3.00 [2.42–3.60]	2.56 [2.13–3.21]	2.79 [2.45–3.49]	2.88 [2.55–3.55]	3.02 [2.40–3.61]	NS
HDL cholesterol (mmol/L)	1.13 [0.96–1.34]	1.34 [1.08–1.49]	1.26 [1.04–1.41]	1.16 [0.97–1.42]	1.12 [0.95–1.32]	0.014
Triglycerides (mmol/L)	1.39 [1.03–1.98]	1.21 [0.72–1.88]	1.03 [0.83–1.59]	1.39 [1.07–1.97]	1.43 [1.05–2.04]	<0.001
Systolic blood pressure (mmHg)	134 [120–148]	130 [116–138]	130 [120–140]	140 [122–146]	134 [120–150]	NS
Diastolic blood pressure (mmHg)	80 [80–90]	80 [78–90]	80 [76–90]	82 [79–90]	82 [80–90]	NS
eGFR (mL/min/1.73 m <sup>2</sup> )	81 [71–94]	68 [66–84]	84 [75–98]	76 [64–90]	82 [71–94]	0.014
M-clamp (μmol/min/m <sup>2</sup> BSA)	604 [380–865]	1281 [1183–1567]	1326 [1202–1454]	516 [352–683]	546 [352–754]	<0.001
Beta-cell – DC (pmol/m <sup>2</sup> BSA)/(mmol/l/min)	444 [52–958]	2328 [1578–3211]	458 [0–768]	1762 [1356–2202]	342 [0–768]	<0.001
Beta-cell – PC (pmol/m <sup>2</sup> BSA)/(mmol/l/min)	47 [25–76]	127 [119–157]	49 [29–72]	140 [117–180]	40 [22–65]	<0.001

Abbreviations: BSA = body surface area. OGTT = oral glucose tolerance test. LDL = low density lipoprotein. HDL = high density lipoprotein. GFR = glomerular filtration rate. DC = derivative control of insulin secretion. PC = proportional control of insulin secretion. PG = plasma glucose. BG = blood glucose. NS = not significant. *p* values from Kruskal Wallis analysis of variance. Median [interquartile range].

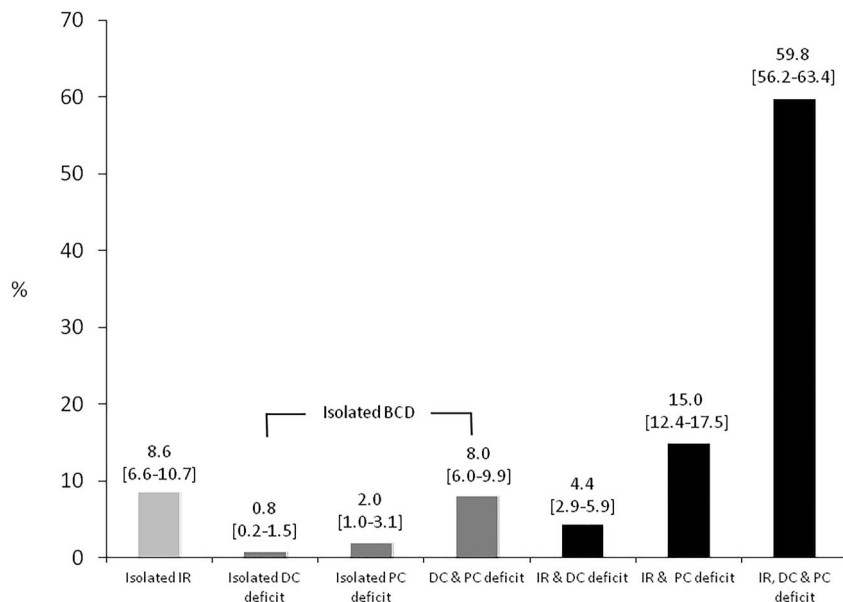
or, alternatively, waist circumference, were included in the various models. No difference in results was found when we excluded from analyses the few subjects who had been treated with glucose lowering agents in the weeks before testing and who underwent at least of 1-week of wash-out or when we excluded the 59 subjects with HbA1c >8.5%. All these results are reported in supplementary Tables in Supporting Information S1.

## 4 | DISCUSSION

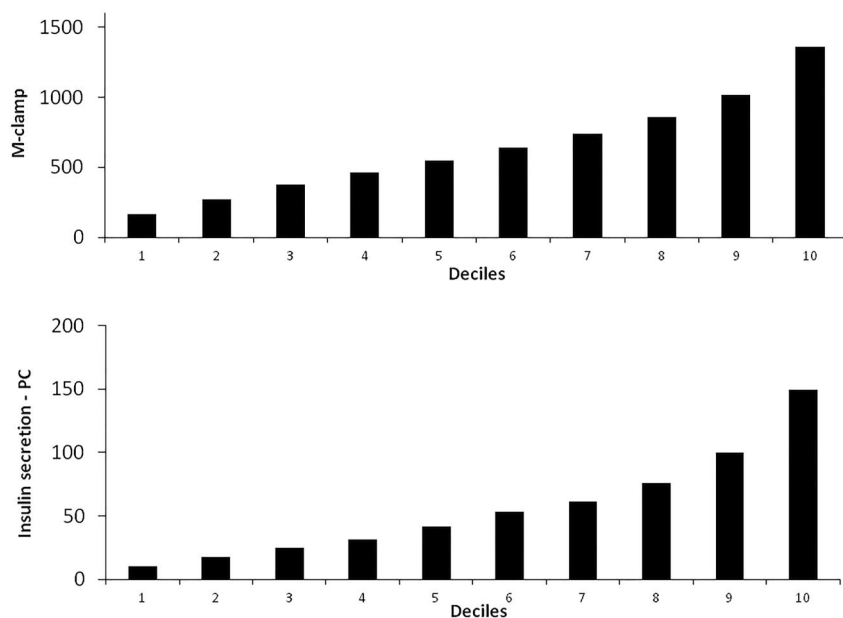
Our data confirm in newly diagnosed patients and with state-of-the-art techniques a time honoured tenet: BCD and IR coexist in most patients with type 2 diabetes. Nevertheless, we found that a

significant fraction of them (~1 out of 5) had only BCD (~1 out of 10) or only IR (~1 out of 10). Interestingly, patients showing a defect in DC (alone or, more frequently, combined with IR) but not a defect in PC were less represented than those showing a defect in PC (alone or, more frequently, combined with IR) without a defect in DC. However, the majority of patients (~70%) had a defect in both DC and PC and among them most had also IR (~90%).

The dynamic range of BCD and IR was quite broad, covering one order of magnitude. A number of subjects were 5 to 10-fold more insulin resistant than others and/or had an impairment of insulin secretion 5 to 10-fold more severe than others. Therefore, layering the subjects according to the degree (mild, moderate, severe) of metabolic defects seemed a sensible choice. When subjects were arbitrarily stratified into nine metabolic combinations of mild,



**FIGURE 1** Frequency of patients with type 2 diabetes with the presence of insulin resistance (IR) and/or beta-cell defect (beta-cell dysfunction (BCD)), consisting of a deficit of derivative control (DC) and/or proportional control (PC) of insulin secretion. 95% confidence intervals (CI) are in brackets



**FIGURE 2** Median of M-clamp values ( $\mu\text{mol}/\text{min}/\text{m}^2$  Body Surface Area [BSA]; upper panel) and proportional control (PC) values ( $\text{pmol}/\text{m}^2$  BSA/(mmol/l/min; lower panel) after stratification into deciles

moderate or severe BCD (e.g., PC) and mild, moderate or severe IR (M-clamp), their frequencies were quite similar (~10% each). In other words, all possible combinations of IR and BCD were similarly represented among patients. On the other hand mean M-clamp value did not differ in most and least beta-cell deficient subjects and PC values did not differ in most and least insulin resistant patients. These findings challenge the old concept that the more insulin deficient subjects have a milder defect in insulin sensitivity and vice versa. On the contrary, our data support the concept that the quantitative expression of each of the two major pathogenic defects of type 2 diabetes is poorly related to the expression of the other one.

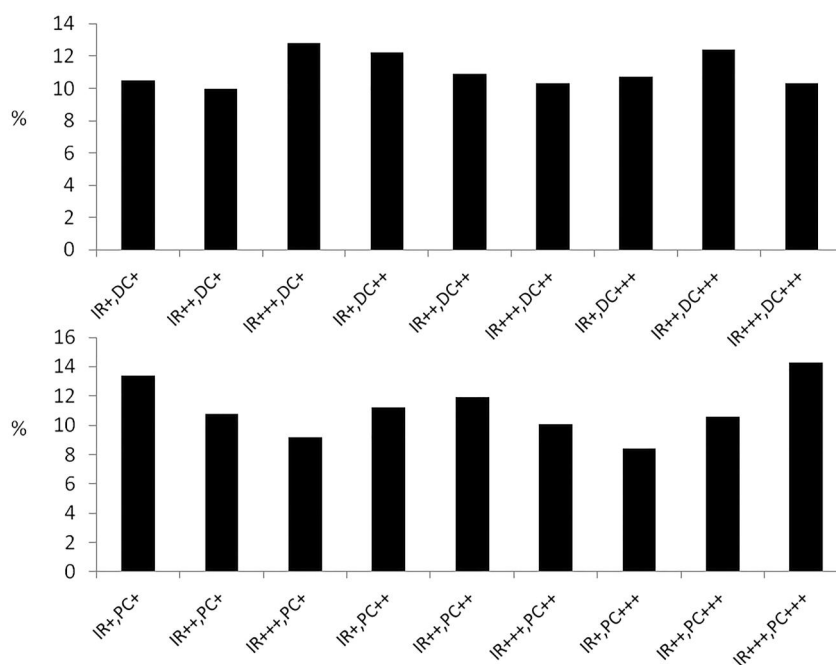
Beta-cell dysfunction was associated with the various parameters of glucose control more strongly than IR. This finding is compatible with a prominent role of BCD over IR in causing and/or

maintaining hyperglycemia in newly diagnosed type 2 diabetes. The association of PC with parameters of glucose control was stronger than DC, possibly because PC accounts for the vast majority of total insulin output during an OGTT.

Beta-cell dysfunction and IR were investigated in previous studies on large series of newly diagnosed patients. However, surrogate methods in the assessment of insulin sensitivity and/or secretion were generally used in these studies. Yet, the percentage of patients with normal insulin sensitivity or secretion was rarely reported. Moreover, these studies did not focus on the spread of IR and BCD among patients, their aggregation in the single individual and their relative role in causing/sustaining hyperglycemia. Levy et al<sup>25</sup> in the Belfast Diet Study identified 3 subgroups according to a more or less severe impairment of insulin secretion detected by the



**FIGURE 3** Frequency of combination of a mild (+), moderate (++) or severe (+++) insulin resistance (IR) and deficit of derivative control (DC; upper panel) or proportional control (PC; lower panel) of insulin secretion in patients with newly diagnosed type 2 diabetes



**TABLE 2** Beta-standardized regression coefficients in multivariable regression analysis with glycaemic parameters as dependent variables and insulin sensitivity (M-clamp) and derivative control (DC) (a) or proportional control (PC) (b) of insulin secretion as independent variables in the model. Additional variables included in the regression model were age and gender. PG = plasma glucose. BG = blood glucose. DC = derivative control of insulin secretion. PC = proportional control of insulin secretion. *p* values are in parenthesis

<b>(a)</b>						
Independent variables	HbA1c	Fasting PG	2-h OGTT PG	Pre-prandial BG	Post-prandial BG	Prandial increase in BG
Age	-0.075 (NS)	0.043 (NS)	0.047 (NS)	0.007 (NS)	0.028 (NS)	0.034 (NS)
Sex	0.004 (NS)	-0.008 (NS)	-0.017 (NS)	-0.025 (NS)	0.008 (NS)	0.038 (NS)
M-clamp	-0.215 (<0.001)	-0.292 (<0.001)	-0.345 (<0.001)	-0.268 (<0.001)	-0.301 (<0.001)	-0.196 (<0.001)
DC	-0.179 (<0.001)	-0.143 (<0.001)	-0.222 (<0.001)	-0.117 (0.004)	-0.172 (<0.001)	-0.157 (<0.001)
<b>(b)</b>						
Independent variables	HbA1c	Fasting PG	2-h OGTT PG	Pre-prandial BG	Post-prandial BG	Prandial increase in BG
Age	-0.029 (NS)	0.087 (0.004)	0.102 (<0.001)	0.038 (NS)	0.065 (NS)	0.058 (NS)
Sex	0.058 (NS)	0.058 (NS)	0.060 (0.017)	0.042 (NS)	0.073 (0.035)	0.073 (0.035)
M-clamp	-0.162 (<0.001)	-0.233 (<0.001)	-0.272 (<0.001)	-0.226 (<0.001)	-0.258 (<0.001)	-0.172 (<0.001)
PC	-0.496 (<0.001)	-0.556 (<0.001)	-0.687 (<0.001)	-0.498 (<0.001)	-0.530 (<0.001)	-0.314 (<0.001)

Abbreviations: NS = not significant.

Homeostasis Model Assessment (HOMA).<sup>26</sup> Stidsen et al<sup>27</sup> investigated with the same surrogate method a very large number of newly-diagnosed Danish patients (80% already on treatment) and found that those with type 2 diabetes could be grouped into “insulinopenic”, “classic” and “hyperinsulinemic”. In the IR and Atherosclerosis Study<sup>28</sup> insulin sensitivity and secretion were measured by frequently sampled intravenous glucose tolerance test, which is certainly more accurate than the HOMA in the assessment of insulin secretion but suboptimal in the assessment of insulin sensitivity. The authors of this study found that less than 5% of newly diagnosed Caucasians patients with type 2 diabetes were not insulin resistant

but did not provide any information on the proportion of those without a beta-cell defect. In a recent paper by Ahlqvist et al,<sup>29</sup> 5 type 2 diabetes subgroups were identified by cluster analysis and the combined use of HOMA and few clinical features. In a paper by Zaharia et al<sup>30</sup> data generated by hyperinsulinemic euglycemic clamp and C-peptide response to intravenous glucose were included in a similar cluster analysis, confirming with more sophisticated techniques the existence of the subgroups described by Ahlqvist et al.<sup>29</sup> The same clusters were observed by Dennis et al,<sup>31</sup> who used the HOMA for investigating insulin secretion and sensitivity, and by Bizzotto et al<sup>32</sup> who used mathematical models applied to mixed

meal tests for the assessment of both insulin secretion and sensitivity.

Comprehensive identification of sub-phenotypes is beyond the scope of the present study. Nevertheless, we confirm with state-of-the-art techniques that type 2 diabetes is probably a too simplistic nosologic definition for subjects who are profoundly different in BCD and/or IR. The time has probably come for a more detailed categorisation of subjects diagnosed with type 2 diabetes, as also suggested by others.<sup>33,34</sup> An assessment of insulin secretion and sensitivity should be part of this precise diagnostics. Tools, however, should be suitable for clinical practice, as pointed out by Dennis et al.<sup>31</sup> Euglycemic hyperinsulinemic clamp and mathematical modelling of OGTT, that is, state-of-the-art techniques we used in this study, cannot be proposed for clinical practice but, in an exploratory study like ours, they provided a sensible improvement in the quantitative pathophysiologic portrait of type 2 diabetes and might contribute to the current discussion about the perspectives of precision medicine. Homeostasis Model Assessment or simple parameters derived from standard OGTT could be proposed as they also predict the risk of type 2 diabetes and cardiovascular disease.<sup>35,36</sup> However, an international standardisation of insulin and C-peptide assays would be a prerequisite and cutoff values should be established. Whatever these tools are, cluster analysis for assigning patients to subgroups would not be a suitable approach in clinical practice. On the other hand, our data support the concept that the great heterogeneity of type 2 diabetes could be better explored using a dimensional rather than a categorical approach. In other words, rather than categorise patients within "clusters", it could be more precisely informative and also more convenient to individually define them by an assessment of the main pathogenetic mechanisms, each considered as a continuous variable.

Strengths of our study are the large sample examined in a single centre with state-of-the-art techniques for the assessment of IR and BCD, the evaluation of different components (derivative and PC) of beta cell response of glucose, the use of several parameters to quantify hyperglycemia. A further strength is that subjects with autoimmunity (i.e., Latent Autoimmune Diabetes of the Adult) were excluded. All subjects included in the study had an assessment of anti-GAD antibodies. In our population we have also recently examined over 90% of common genetic variability in nine monogenic diabetes genes, without finding any evidence that some patients could have MODY.<sup>37</sup>

Weaknesses of this study are the exclusion of non-Caucasian subjects and of patients older than 75 years, making our data not fully generalisable. In patients of more advanced age the pathophysiology of the disease might be different. Another limit is that we have not used a glucose tracer to dissect out the relative roles of liver and peripheral tissues in determining whole body IR. A further limitation may be that time of diagnosis of T2DM almost never corresponds to time of onset of the disease.<sup>38</sup> Therefore, we cannot exclude that the proportions of subjects with IR and/or BCD might be different at time of true onset of the disease. However, several studies have shown that the decline in beta-cell function more than

the deterioration of IR precipitates the onset of hyperglycemia and T2DM.<sup>39,40</sup> Yet, as in any other test of beta cell function, the parameters quantified by the OGTT minimal model are influenced to some degree by insulin sensitivity.<sup>15,18</sup> Finally, as this is a cross-sectional study, we cannot exclude that the relation between BCD and IR and their relative contribution to hyperglycemia might change in the years following diagnosis. Indeed, beta-cell function declines over time in T2DM.<sup>25,41</sup> The longitudinal assessment of this cohort is ongoing and might clarify this point.

We used arbitrary cutoff values for the definition of BCD and IR. These values seemed reasonable as the 25<sup>th</sup> percentile is largely used in the literature for many continuous variables. However, these values might be arbitrarily set at 10<sup>th</sup> or 20<sup>th</sup> percentile, with obvious reduction in the number of patients assigned to BCD and/or IR categories. Yet, different 25<sup>th</sup> percentile values might be identified in different populations of nondiabetic subjects. Extrapolation of our cutoff values to other populations should be made with great caution.

In conclusion, BCD and IR are expressed in newly diagnosed type 2 diabetes with wide variability, ranging from mild to moderate and severe. The two abnormalities aggregate in the same individual without a trend for worse BCD in those with less pronounced IR and vice versa. The pathogenic role of BCD seems to be greater than IR in causing/sustaining hyperglycemia in newly diagnosed type 2 diabetes. Therefore, quantifying the severity of the two defects could help the physician in selecting the most appropriate personalised treatment of people with newly diagnosed type 2 diabetes. This exploratory study might be instrumental to promote the development of new clinical diagnostic tools for IR and BCD which conjugate simplicity, reliability and affordability.

#### AUTHOR CONTRIBUTION

Enzo Bonora, Maddalena Trombetta and Riccardo C. Bonadonna designed the protocol and planned statistical analyses. All authors collected data and contributed to their interpretation and discussion. Federica Moschetta and Monica Zardini performed laboratory work. Maria Linda Boselli modelled data of insulin secretion. Lorenza Santi made data entry and statistical analyses. Enzo Bonora drafted the manuscript, Maddalena Trombetta and Riccardo C. Bonadonna edited it and all authors reviewed and approved it and agree to be accountable for all aspects of work. Enzo Bonora is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

#### ACKNOWLEDGEMENTS

The superb assistance of the nurses of the Division of Endocrinology, Diabetes and Metabolism of the Hospital Trust of Verona in performing metabolic studies is greatly acknowledged. The study was supported by grants from the Italian Ministry of the Education, University and Research (PRIN 2009WYP4AS to EB; PRIN 2015373Z39\_002 to EB; PRIN 2015373Z39\_004 to RCB; PRIN 2010098WFZ2\_003 to RCB), the University of Verona (scientific



achievement-based grants to EB,MT,RCB), the University of Parma (scientific achievement-based grants to RCB), the Foundation of the European Association for the Study of Diabetes (EFSD/Novartis grant to RCB), the Foundation of the Italian Diabetes Society (Research Grant to MT).

Enzo Bonora, Maddalena Trombetta and Riccardo C. Bonadonna designed the protocol and planned statistical analyses. All authors collected data and contributed to their interpretation and discussion. Federica Moschetta and Monica Zardini performed laboratory work. Maria Linda Boselli modelled data of insulin secretion. Lorenza Santi made data entry and statistical analyses. Enzo Bonora drafted the manuscript, Maddalena Trombetta and Riccardo C. Bonadonna edited it and all authors reviewed and approved it and agree to be accountable for all aspects of work. Enzo Bonora is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

All data generated or analysed during this study are included in this published article.

Part of these data were presented at the 75<sup>th</sup> Scientific Sessions of the American Diabetes Association (Boston, June 5–9, 2015) and the 51<sup>th</sup> Annual Meeting of the European Association for the Study of Diabetes (Stockholm, September 14–18, 2015). Part of these data were included in the PhD thesis of Dr. Marco Dauriz.

Open Access Funding provided by Università degli Studi di Verona within the CRUI-CARE Agreement.

## CONFLICTS OF INTEREST

None of the authors has anything to disclose which is pertinent to this paper.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

## ETHICS STATEMENT

The protocol was approved by the local Ethics Committee and is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (n. NCT01526720).

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## TRANSPARENT PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/dmrr.3558>.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Bonora E, Trombetta M, Dauriz M, et al. Insulin resistance and beta-cell dysfunction in newly diagnosed type 2 diabetes: Expression, aggregation and predominance. *Verona Newly Diagnosed Type 2 Diabetes Study 10*. *Diabetes Metab Res Rev*. 2022;38(7):e3558. <https://doi.org/10.1002/dmrr.3558>