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Clinical Research Study

Cardiovascular risk, fatty liver disease, glucose and insulin curve among prediabetes phenotypes in Peruvian population

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ABSTRACT

Aims: To describe the cardiovascular risks, fatty liver disease, and glucose and insulin curve among prediabetes phenotypes (PPh) in Peruvian population.
Methods: A study was carried out using a secondary database of a series of patients with identified risk factors for diabetes mellitus type 2 in one clinic in Lima, Peru. Patients were divided according with the OGTT in impaired glucose 2h or IGT(Pph1), impaired fasting glucose or IFG(Pph3) or both(Pph2).
Results: 259 patients were identified for analysis, 149 of whom had normal OGTT, 94 had prediabetes (36.3%), and 16 diabetes (6.2%). We found that 37(39.4%), 37(39.4%) and 20(21.2%) presented Pph1, Pph-2 and Pph-3 respectively. Most of the cardiovascular risks and hepatic function comparison showed no difference in our study sample groups. However, we found that Pph2 showed significantly higher abnormalities in HDL-c, triglycerides, hepatic steatosis, and HOMA-IR compared with normal OGTT group ($p < 0.05$). Interestingly, this difference was not seen with the other phenotypes. Also, hepatic steatosis was higher in Pph2 compared to Pph3 ($p < 0.05$). HOMA-IR was high in Phenotype 2 compared with Phenotype 1. Regarding hepatic steatosis, this was high in all prediabetes phenotypes, however we found this to be of statistical significance in Pph2 compared to Pph3 ($p < 0.01$).
Conclusions: In general, prediabetes phenotypes show a similar association with cardiovascular risk factors and hepatic steatosis, however, Pph2 show more differences in specific comparisons. We believe that this study is a starting point for further investigation to understand prediabetes in Peruvian population and be able to improve disease risk stratification.

Introduction

According to the World Health Organization, it is estimated that there are approximately 422 million people who suffer from type 2 diabetes mellitus around the world (T2DM), estimating that 1.5 million of the deaths in the world are due to this disease.[1] Projections have determined that by 2040 this figure will increase to 642 million.[2] T2DM has a natural history that can be identified many years beforehand in the vast majority of affected individuals. Prediabetes, which includes a group of alterations in blood glucose levels, is an intermediate condition between euglycemia and T2DM and consists of elevated fasting glucose levels and / or an altered oral glucose tolerance test (OGTT) where glycaemia at two hours is elevated but does not meet the criteria to be considered T2DM.[3,4] In Peru, based on a population study, it is estimated that the prevalence of impaired fasting glucose is 22.4%.[5] However, a Peruvian expert consensus suggested this could be an approximate estimation of prediabetes prevalence in the country underestimated by not using OGTT.[6]

There are several risk factors that should be taken into consideration for developing T2DM. An individual who will develop this disease, frequently presents obesity or overweight in its early stages with a genotype unfavourable, Over time, they may develop physical and metabolic changes such as an increase in waist circumference which is a consequence of the increased accumulation of adipose tissue in its viscera, increase in its blood pressure, increase in small and dense low-density lipoprotein cholesterol (LDL-c) particles, elevation of triglycerides that goes parallel to the decrease in high-density lipoprotein cholesterol (HDL-c),[7,8] elevation of uric acid and also can experience the increas-

Abbreviations: TD2M, Type 2 Diabetes Mellitus; OGTT, Oral glucose tolerance test; LDL-c, Low-density lipoprotein cholesterol; HDL-c, High-density lipoprotein cholesterol; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; GOT, Glutamic oxaloacetic transaminase; GPT, Glutamic pyruvic transaminase; HOMA-IR, Homeostatic model assessment ofinsuline resistance index; HOMA-β, Homeostatic model assessment of β-cell function index; BMI, Body mass index.

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ingly frequent accumulation of drops of fat in the liver leading to the so-called non-alcoholic fatty liver disease.[9–11] All these changes can be evidenced from the clinical onset of diabetes[12] or for many years afterwards.[13] Thus, cardiovascular risk is increased in these subjects, even long before the onset of diabetes itself.[14]

Prediabetes metabolic phenotypes has been described in previous studies.[15–19] Although the denomination phenotypes can be discussed and refuted, this is used by clinicians and researchers to describe the heterogeneity in the pathophysiological alterations of the glucose metabolism.[16] In general, the alterations are described as follows: isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), or both IFG/IGT as prediabetes metabolic phenotypes.[17] For practicality, we will refer to these biochemical characteristics as phenotypes.

These changes can be evaluated through the glucose tolerance curve, which can be monophasic or biphasic, and can provide us with a vast information about insulin sensitivity at the muscle level, taking into consideration that the biphasic curve is closely associated with normal glucose tolerance.[20]

Improved understanding of these features and precise phenotyping of prediabetes could help to improve stratification of disease risk. Thus, the present study aims to describe the cardiovascular risk factors, fatty liver disease, and glucose and insulin curve among metabolic prediabetes phenotypes in Peruvian population.

Materials and methods

Study design and study location

A cross-sectional study was carried out using an anonymous secondary database of patients who attended an endocrinology clinic for 18 months (2016–2017) in the city of Lima, Peru.

Participants

All patients were over 18 years of age and had an indication for OGTT based on the following criteria: (a) Family history of T2DM: obese diabetic father/mother/brother/son, (b) Obesity or significant overweight (BMI ≥ 27) or (c) fasting hyperglycemia (100–125 mg/dl).

Patients with the following criteria were excluded id: (a) they received insulin-sensitizing drugs (metformin) or anorectics during the previous 6 m, (b) they received drugs that alter the OGTT (corticosteroids, loop diuretics, beta-blockers), (c) they were hospitalized in the last 6 months, (d) underwent bariatric surgery, (e) pregnant, (f) chronic kidney failure, liver cirrhosis, clinically manifest respiratory or cardiac failure, (g) HIV positive, (h) chemotherapy.

Definitions of variables

Patients underwent OGTT where glucose and insulin were measured at 0, 60 and 120 min. The test was done using load dose of 75 g of anhydrous glucose.

They were classified according to the prediabetes phenotypes previously described in the literature[18] as follows: (a) Phenotype 1 (Pph1): defined as the group that presented fasting blood glucose <100 mg/dl and blood glucose 2h after the OGTT between 140–199 mg/dl; (b) Phenotype 2 (Pph2): defined as fasting glycemia of 100–125 mg/dl and 2h glycemia of the OGTT between 140–199 mg/dl; and c) Phenotype 3 (Pph3): defined as fasting glycemia 100–125 mg/dl and 2h glycemia of the OGTT <140 mg/dl.

The demographic variables evaluated were age and gender. Blood pressure, body mass index (BMI), waist circumference, HbA1c, total cholesterol, LDL-c, HDL-c, non-HDL-c, triglycerides, uric acid, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were reported as continuous and categorical variables.

Glucose, transaminases, and lipids measurements were analysed using the fully automated analyser Cobas 6000 (Roche Laboratory). Insulin was analysed using chemiluminescence (Immulite Machine). HbA1c was analysed using capillary electrophoresis (Capyllaris 2, Sebia).

For waist circumference, the cut-off point defined by Aschner et al.[21] was validated in an expert consensus for Peruvian population where increased waist circumference was agreed to be defined as: more than 94 cm in men and more than 90 cm in women.[22]

We calculated the Homeostatic model assessment for assessing β-cell function and insulin resistance (HOMA-IR) and index of insulin secretory function derived from fasting plasma glucose and insulin concentrations (HOMA-β).[23] The presence of hepatic steatosis was defined based on the findings in an abdominal ultrasound. Diagnosis of fatty liver was based on the report of a registered ultrasound medical radiologist, regardless of the severity of the hepatic steatosis. Echographic characteristics included increased echogenicity in liver parenchyma, signal attenuation or loss of the distal image, increased liver volume depending on the size and age of the patient, and blunt edges of the liver.

It is important to emphasize that the missing data represented less than 5% of all variables except for insulin. Insulin results were missed in more than 20% of the sample for which these results should be interpreted with caution.

Analysis of data

We evaluate the distribution of variables using numerical and graphical methods. We included all observations for analysis. Variables that were not normalized after transformation were analysed in their original form, using non-parametric tests. Variables with normal distribution were summarized using the mean and standard deviation (geometric mean and geometric standard deviation were used for logarithmically transformed numerical variables). Normality was analysed by Kolmogorov–Smirnov test and Shapiro Wilk test.

For the multivariable analysis, we divided the sample in groups according with OGTT results. We compared the distribution of age, anthropometric, metabolic and liver function and steatosis parameters between the study groups using an Analysis of Variance (ANOVA) or the Kruskal-Wallis test, as appropriate. The statistical tests were two-tailed and a significance level of 5% was considered relevant ($p < 0.05$). We have included post-hoc Bonferroni analysis to compare the different groups. All statistical analyses were performed using Stata 16.0. (StataCorp LP, College Station, Texas, United States).

Additionally, based on the results of the OGTT, we drew glucose and insulin curves based on the data of the OGTT results (0, 60, 90 min) that are presented as figures.

Ethical criteria

Patient data were part of a totally anonymized outpatient registry. Thus, the present study was exempted from review by a local ethics committee.

Results

A total of 259 participants were eligible for inclusion in the final analysis. The mean age was 46 years (SD 14.4) and the majority were women (66%). The main characteristics are described in Table 1. Regarding the indication for OGTT, it was observed that 207 patients (75.6%) had at least BMI greater than or equal to 27; 114 patients (41.6%) had at least family history of T2DM and 72 patients (26.3%) had at least an abnormal fasting hyperglycemia.

All patients had a OGTT performed. Regarding the results, 149 (57.5%) had a normal OGTT, 94 patients had prediabetes (36.3%), and 16 had DM2 (6.2%). According to the previously described definitions of prediabetes phenotypes used in this study, we found that 37 (39.4%), 37 (39.4%) and 20 (21.2%) patients presented Pph1, Pph2 and Pph3 respectively (Fig. 1).

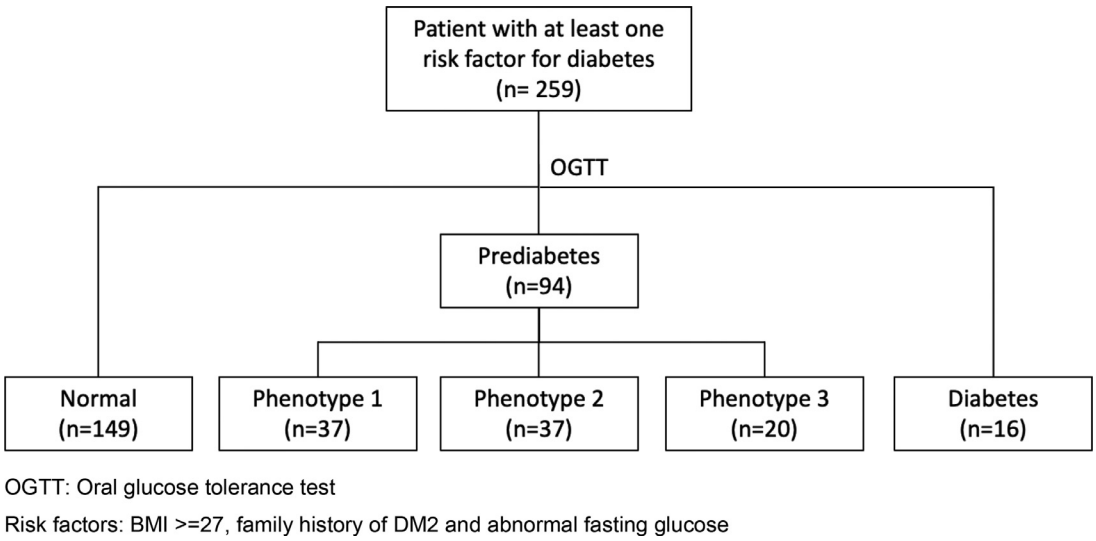

Fig. 1. Flowchart of diagnosis based on OGTT results, OGTT: Oral glucose tolerance test, Risk factors: BMI >=27, family history of DM2 and abnormal fasting glucose.

Table 1
Main characteristics of study population.

	Total (N = 259)
Age (years), mean (SD)	46.0 (±14.4)
Woman, n(%)	171 (66.0%)
BMI, mean (SD)	31.4 (±5.1)
Waist circumference (cm), mean (SD)	98.5 (±12.6)
Systolic arterial pressure (MmHg), mean (SD)	126.3 (±13.1)
Diastolic arterial pressure (MmHg), mean (SD)	77.9 (±7.8)
HbA1c (%), mean (SD)	5.7 (±0.5)
HOMA-IR	3.8 (±2.9)
HOMA-β	215 (±124.0)
Total cholesterol (mg/dl), mean (SD)	196.3 (±39.8)
LDLc (mg/dl), mean (SD)	119.5 (±34.8)
HDLc (mg/dl), mean (SD)	46.9 (±12.4)
Non-HDL Cholesterol (mg/dl), mean (SD)	148.2 (± 40.8)
Triglycerides (mg/dl), mean (SD)	161.4 (±110.7)
Uric Acid (mg/dl), mean (SD)	5.3 (±1.3)
Hepatic Steatosis, n(%)	160 (64.5)
GOT (U/l), mean (SD)	36.3 (±27.9%)
GPT (U/l), mean (SD)	36.7 (±28.0)
Risk factors	
At least presented BMI >=27, n(%)	207 (75.6%)
At least presented family history of T2DM (%)	114 (41.6%)
At least presented abnormal fasting glucose (%)	72 (26.3%)

BMI: Body mass index, LDLc: Low-density lipoprotein cholesterol, HDLc: High-density lipoprotein cholesterol, GOT: glutamic oxaloacetic transaminase, GPT:glutamic pyruvic transaminase, SD: Standard deviation.

Table 2 compares the cardiovascular risk factors and hepatic steatosis risk of the five groups. Except for hepatic steatosis, all the comparisons used ANOVA with Bonferroni correction to be able to identify the different means. Additionally, we described the global p that describes which of the variables have at least on comparison that is different. Based on this table, we can observe that total cholesterol, HDL-c, triglycerides, HOMA-IR and hepatic steatosis showed at least one group comparison that was different.

Interestingly, Pph2 showed lower HDL-c compared with the groups with normal OGTT (p = 0.04) but the other comparisons were similar. Triglycerides also were significantly higher in Pph2 versus the group with normal OGTT (p = 0.02). The other comparison statistically different in triglycerides were comparisons with diabetes group compared with Phenotype 1 (p = 0.02), Pph13 (p = 0.01) and Normal OGTT ($p < 0.01$). However, regarding triglycerides diabetes and Pph2 showed no differences.

Hepatic steatosis was more frequent in Pph2 compared with the group with normal OGTT ($p < 0.01$) and Pph3 (p = 0.04). As expected, hepatic steatosis was more frequent in the groups with diabetes compared with the group with normal OGTT ($p < 0.01$)

Calculated HOMA-IR showed was higher in Pph2 and Pph3 compared with the group with normal OGTT ($p < 0.01$ and p = 0.01 respectively). Pph2 showed higher HOMA-IR compared with phenotype 1 ($p < 0.01$).

LDL-c, Non-HDL-c cholesterol, BMI, waist circumference, arterial pressure, transaminases and HOMA-β variables showed no difference between the groups in our study sample.

Table 3 shows groups comparisons of glucose and insulin results that are shown graphically in the Fig. 2. Regarding the prediabetes phenotypes comparisons, we can see that fasting glucose were higher in Pph3 and Pph2 compared with Pph1. However, these two groups were similarly high compared to each other.. Insulin curves should be interpreted carefully since this was a measurement with the higher missing data from our study.

Discussion

To our knowledge, this is the first study with the objective to describe the different prediabetes phenotypes in Peruvian population with risk factor for DM2. In our study, we defined three different prediabetes phenotypes. Additionally, we included groups with normal OGTT and diabetes for comparison. Most of the cardiovascular risk and hepatic function comparison were not different between the groups. However, we found that Pph2 presented with statistical differences regarding HDL-c, triglycerides, hepatic steatosis, and HOMA-IR compared with the group with normal OGTT. Interestingly, this difference was not seen with the other phenotypes. Regarding hepatic steatosis, this was high in all prediabetes phenotypes, however we found this to be of statistical significance in Pph2 compared to Pph3. It is worth noting that in patients with normal OGTT presented 55.9% of hepatic steatosis which is very high compared with previous documented findings in general population.[24] This finding could be related insulin resistance in this sample with high risk factors of DM2.

Regarding HOMA-IR, the mean in our population, including normal OGTT, showed a high index greater than 2.8. Although some authors consider a cut-off of 2.8 as an altered value of HOMA-IR.[25] We considered the definition of a study based on a Chilean specific population that

Table 2
Comparisons of cardiovascular risk factors and hepatic steatosis between groups.

	Group comparisons														
	Normal (N = 149)	Pph1 (N = 37)	Pph2 (N = 37)	Pph3 (N = 20)	DM2 (N = 16)	N vs Pph1	N vs Pph2	N vs Pph3	Pph1 vs Pph2	Pph1 vs Pph3	Pph2 vs Pph3	DM2 vs Pph1	DM2 vs Pph2	DM2 vs Pph3	N Vs DM2	Global p
Total cholesterol (mg/dl), mean (SD)	191 (±37.2)	196.3 (±6.3)	202.9 (±6.9)	198 (±8.2)	224.7 (±13.3)	1	1	1	1	1	1	0.16	0.64	0.43	0.01	0.02
LDLc (mg/dl), mean (SD)	117.3 (±32.9)	119.0 (±6.5)	124.7 (±6.8)	119.3 (±8.3)	135.3 (±40.7)	1	1	1	1	1	1	1	1	1	1	0.50
HDLc (mg/dl), mean (SD)	47.9 (±11.9)	48.1 (±12.3)	41.1 (±8.7)	49.3 (±18.3)	42.9 (±12.9)	1	0.04	1	0.20	1	0.28	1	1	1	1	0.03
Non-HDL Cholesterol (mg/dl), mean (SD)	143.1 (±37.8)	149 (±40.1)	159.8 (±42.8)	144.8 (±40.5)	143.1 (±37.8)	1	0.32	1	1	1	1	0.27	1	0.25	0.03	0.01
Triglycerides (mg/dl), mean (SD)	138.3 (±75.8)	173.8 (±92.4)	198.9 (±137.3)	155.6 (±101.6)	271 (±231.8)	0.67	0.02	1	1	1	1	0.02	0.23	0.01	0.00	<0.01
BMI, mean (SD)	30.9 (±4.7)	31.2 (±4.5)	33.1 (±6.9)	31.9 (±4.9)	31.5 (±4.7)	1	0.27	1	1	1	1	1	1	1	1	0.27
Waist circumference (cm), mean (SD)	97.4 (±12.1)	97.7 (±11.2)	102 (±13.89)	98.4 (±16.1)	103.9 (±12.3)	1	0.54	1	1	1	1	0.98	1	1	0.49	0.14
Systolic arterial pressure (MmHg), mean (SD)	124.1 (±12.3)	128.7 (±13.3)	129.6 (±13.1)	127.9 (±11.8)	131.2 (±17.8)	0.65	0.25	1	1	1	1	1	1	1	0.40	0.05
Diastolic arterial pressure (MmHg), mean (SD)	77.1 (±7.8)	79.8 (±6.1)	78.8 (±7.4)	78.9 (±8.1)	78.7 (±10.4)	0.77	1	1	1	1	1	1	1	1	1	0.36
Hepatic Steatosis n(%)**	80 (55.9)	24 (70.6)	32 (86.5)	12 (63.2)	12 (80)	0.12	<0.01	0.55	0.10	0.55	0.04	0.49	0.55	0.30	<0.01	<0.01
HOMA-IR *	2.8 (±1.9)	3.05 (±2.1)	7.3 (±3.6)	5.2 (±2.9)	6.2 (±4.7)	1	<0.01	0.01	<0.01	0.65	0.26	0.64	1	1	0.22	<0.01
HOMA-B *	198.42 (±127.6)	238.2 (±170.1)	256.7 (±112.1)	202.7 (±118.7)	135.5 (±44.4)	1	1	1	1	1	1	1	1	1	1	0.48
GOT (U/l), mean (SD)	26 (±17.4)	26.2 (±2.7)	20 (±2.6)	29.5 (±5.1)	28.8 (±3.5)	1	1	1	1	1	1	1	1	1	1	0.82
GPT (U/l), mean (SD)	35.2 (±28.7)	35.0 (±3.6)	39.9 (±4.6)	42.4 (±10.3)	40.9 (±5.7)	1	1	1	1	1	1	1	1	1	1	0.75

N: Normal OGTT; PPh1: Phenotype 1; PPh2:Phenotype 2; PPh3: Phenotype2; DM2: Diabetes Mellitus type 2; BMI: Body mass index, LDLc: Low-density lipoprotein cholesterol, HDLc: High-density lipoprotein cholesterol, GOT: glutamic oxaloacetic transaminase, GPT: glutamic pyruvic transaminase, SD: Standard deviation, RF: Risk factors
Global p test the hypothesis that there is at least one different comparisons between the groups. All variables, except hepatic steatosis, were analysed using the post-hoc Bronferroni correction.

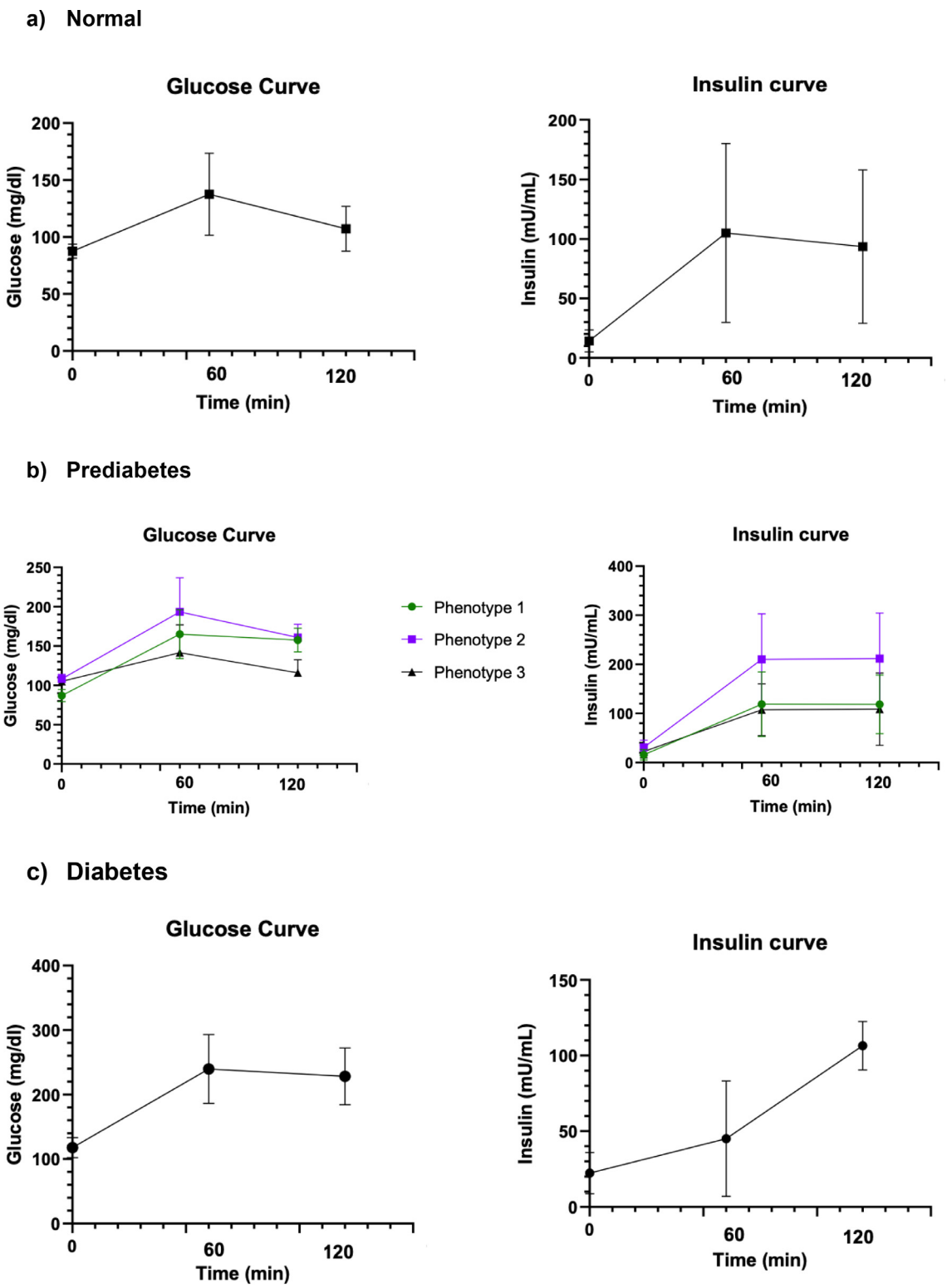

Fig. 2. Glucose and insulin curves during oral glucose tolerance (OGTT).

is more similar to the Peruvian where altered HOMA-IR is described as above 2.7.[26] In the comparisons made, we found that HOMA-IR was higher in Pph2 compared with Pph1. HOMA-IR also was higher in Pph2 and Pph3 compared with normal OGTT. As it has been previously suggested, high HOMA-IR could suggest a higher possibility to prediabetes or even diabetes in this population.[27]

Pph2 had a high HOMA-IR index similar to the group with DM2 at debut (no statistical differences) which could be interpreted as severe global insulin resistance and greater metabolic disturbances which make them more susceptible to evolve to DM2.[28] When comparing these groups, they presented no differences in metabolic alterations, cardiovascular risk factors and frequency of hepatic steatosis. These findings

Table 3
Comparisons of glucose and insulin results from the OGTT between groups.

	Normal (*N* = 149)	Pph1 (*N* = 37)	Pph2 (*N* = 37)	Pph3 (*N* = 20)	DM2 (*N* = 16)	N vs Pph1	N vs Pph2	N vs Pph3	Pph1 vs Pph2	Pph1 vs Pph3	Pph2 vs Pph3	DM2 vs Pph1	DM2 vs Pph2	DM2 vs Pph3	N Vs DM2	Global p
Glucose (mg/dl)																
Basal	87.6 (±6.2)	86.9 (±7.7)	108.3 (±5.7)	105.2 (±5.8)	117.7 (±15.5)	1	<0.01	<0.01	<0.01	<0.01	1	<0.01	<0.01	<0.01	<0.01	<0.01
1 hour	137.6 (±36.1)	165 (±31.2)	193.5 (±43.2)	141.5 (±35.5)	239.8 (±53.4)	<0.01	<0.01	1	0.01	0.25	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
2 hours	107.2 (±19.7)	157.6 (±14.9)	161.02 (±16.6)	115.9 (±16.8)	228.4 (±44.2)	<0.01	<0.01	0.80	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Insulin (mU/mL)																
Basal	14.2 (±9.3)	15.7 (±10.8)	30.9 (±14.6)	22.6 (±13.0)	22.3 (±13.6)	1	<0.01	0.10	0.03	1	0.52	1	1	1	1	<0.01
1 hour	105 (±75.2)	118.7 (±65.8)	210 (±92.7)	107.6 (±52.7)	45 (±38.2)	1	<0.01	1	0.17	1	<0.01	1	0.04	1	1	<0.01
2 hours	93.5 (±64.4)	118.5 (±59.6)	211.7 (±92.9)	108.9 (±73.7)	106.6 (±16.7)	1	<0.01	1	<0.01	1	<0.01	1	0.21	1	1	<0.01

N: Normal OGTT; PPh1: Phenotype 1; PPh2:Phenotype 2; PPh3: Phenotype2; DM2: Diabetes Mellitus type 2Global p test the hypothesis that there is at least one different comparisons between the groups. All variables, except hepatic steatosis, were analysed using the post-hoc Bronferroni correction.

could suggest that Pph2 patients are those with the highest risk of developing DM2.[28]

This same Pph2 is the one with the greatest association with a large number of cardiovascular risk factors and therefore carries the highest pro-atherogenic burden. This is consistent with other studies where these individuals of phenotype 2 have increased cardiovascular morbidity and mortality, stroke or peripheral vascular insufficiency.[29,30] This is due to the presence of atherosclerotic disease and hepatic steatosis which is associated with significant insulin resistance.[31] As evidenced in precious studies, non-alcoholic fatty liver disease is a manifestation of insulin resistance in the liver and is associated with subclinical atherosclerosis[32] and higher risk of evolving to T2DM.[33] There is also an association with increase in HOMA-IR.[34] In our study, fatty liver is present in the majority of patients living with prediabetic and T2DM as well as normoglycemic subjects with risk factors for T2DM.

Regarding OGTT and insulin curves, It is interesting to highlight that in individuals with normal glucose tolerance, insulin levels are elevated both at one hour and two hours, which reflects compensatory hyperinsulinism secondary to insulin resistance.[35] Observing the glycemic and insulin response after the OGTT, it is appreciated that the shape of the curve tends to be monophasic in all groups which is found in agreement of previous studies.[36] In our study, these curves are very similar, even in normal OGTT individuals with risk factors for DM2. On the other hand, patients living with prediabetes maintain the same monophasic shape of the glycemic curve. Both Pph1 and Pph2 have high levels of glycemia at one hour, which translates into a higher risk of evolving to T2DM.[37]

We can see that insulin curve is very similar in these normoglycemic individuals compared with those presented by prediabetic Pph1 and Pph3. We observe that in the case of the Pph2 the insulin release is much higher than the other prediabetes phenotypes, which could be related to the higher degree of insulin resistance evidenced with a higher HOMA-IR and a higher insulin release index HOMA-β. However, there was not statistical difference.

We could also mention that although Pph3 has a higher degree of insulin resistance than Pph1, insulin secretion was very similar, so the the similar insulin curve could be related to the effects of other phenomena such as the degree of insulin sensitivity in peripheral tissues,[38] the effect of incretins[39] and the lack of glucagon suppression.[40,41]

This study has limitations inherent to secondary registration databases. Missing values were less than 5% in all variables except for variables dependant on insulin measurement. It is important to highlight that insulin was only taken in 120 patients (46%) for which insulin results should be considered carefully. We believe that although it should not be representative, it can give an contextualization of the trend in this population. Since original definition of curves need five cut-off points (0, 30, 60, 90 and 120 min), we have made sure we didn't interpret this as a fact, but tendency or approximates. We believe this approximation can give context to the analysis; however we acknowledge the best way to di it will be using the 5 cut-off points. Additionally, there were variables that may have confused the measurements such as weight, waist circumference and blood pressure that could be taken by different health professionals without homogenizing or calibrating the materials for the present study. Although this may give an intra and inter-observer bias, the fact that these measurements were made in a specific clinical practice means that the variability of the health professionals is not high. Additionally, antihypertensive and dyslipidaemia treatment were not analysed and could potentially introduce a confounding factor in our analysis regarding levels of blood pressure and lipid profile. Another important limitation is the generalizability of these results as a case series analysis. For the aforementioned reasons, it is very difficult to extrapolate this study to general population. Nevertheless, we are confident that this can give a starting point for further research and exploration of prediabetes in Peruvian population.

The strengths of the study are that this is the first effort to describe the different phenotypes of prediabetes in the Peruvian population. Although the study has limitations, it is possible to precisely see the trends

of these different phenotypes and to make hypotheses for other studies. The importance of identification of the different phenotypes of prediabetes can lead to a better understanding of this alteration and thus achieve the prevention of the development of diabetes in the country.

In conclusion, all prediabetes phenotypes show a similar incidence of cardiovascular risk factors and frequency of hepatic steatosis., however, phenotype 2 seems to more abnormal in specific comparisons. Limitations of this study prevent us to generalize these results however we believe that this is a starting point for further investigation to understand prediabetes in Peruvian population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CRediT authorship contribution statement

Jesus Rocca-Nación: Data curation, Formal analysis, Writing – review & editing. **Maria Calderon:** Formal analysis, Writing – review & editing.

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