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ORIGINAL ARTICLE

Prediabetes is more than a pre-disease: additional evidences supporting the importance of its early diagnosis and appropriate treatment

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Abstract

Aim To identify Prediabetes (PreD) as early and serious diabetes step using clinical-biochemical characteristics in the population of the Primary Prevention Diabetes Buenos Aires (PPDBA) study.

Methods PPDBA Study evaluated benefits of adopting healthy lifestyles to prevent T2D. It recruited people 45–75 years of age with PreD (impaired fasting glycaemia [IFG], impaired glucose tolerance [IGT] or both, American Diabetes Association criteria), using an opportunistic approach. They completed a FINDRISC questionnaire, and those with a score ≥13 points were invited to participate. When they accepted, we performed an oral glucose tolerance test (OGTT) with a complete lipid profile and HbA1c while physicians completed a clinical history. We recruited 367 persons, and depending on OGTT results, the sample was divided into normals (NGT), PreD, or with diabetes (last one was excluded in our analysis). Data were statistically analyzed using parametric and nonparametric tests and logistic regression to identify parameters associated with PreD.

Results From the recruited ($n = 367$) 47.7% have NGT, 48.5% PreD and 3.8% unknown T2D (excluded). People with PreD were significantly older, with a higher percentage of overweight/obesity, BMI, and larger waist circumference than NGT. They also showed significantly higher fasting and 2 h post glucose load, HbA1c, and triglyceride levels. No significant differences were recorded in the blood pressure, lipid profile though both groups had abnormally high LDL-c values. They also had a larger percentage of TG/HDL-c ratios (insulin resistance indicator) (55% vs. 37.5%). Logistic regression analysis showed that PreD was significant associated with age, waist circumference, and triglyceride above target values.

Conclusion Our findings showed that clinical and biochemical parameters were significantly different between people with PreD and those with NGT. This evidence supports the concept that PreD is a serious dysfunction, which should be early diagnosed and treated properly to prevent its transition to T2D and its complications.

Keywords Prediabetes · OGTT · FINDRISC · Lipid profile · Insulin resistance

Introduction

Type 2 diabetes (T2D) is a serious and growingly costly problem for the health system worldwide, and Argentina is not an exception: its prevalence in the period 2005–2018 grew by 51% (from 8.4 to 12.7%) [1]. Its clinical and metabolic dysfunction is frequently associated with other cardiovascular risk factors (CVRF), facilitating the development and progression of chronic complications which increase its high morbi-mortality and care costs [2, 3].

T2D, its most frequent presentation, has been shown to easier develop in people with a genetic predisposition, exposed to unhealthy habits (unbalanced meal plan and

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physical inactivity) [4]. We and other authors have shown, that careful and regular follow up of these patients at the primary care level effectively keeps them on target for clinical and metabolic control, thereby decreasing their cardiovascular complications [5].

Clinical manifestations of T2D are preceded by a state identified as prediabetes (PreD), characterized by impaired fasting glucose [IFG] - blood glucose level range 100 to 125 mg/dL in fasting- and/or impaired glucose tolerance [IGT] -2-hour post oral glucose load with blood glucose level between 140 to 199 mg/dL [6].

PreD is a heterogeneous state characterized by a different annual progression rate to T2D [7]. Unfortunately, many health-team-care-members consider PreD a pre-disease rather than an early, serious, and costly step of T2D pathology, which merits identical consideration to apply a necessary brake to its continuous increase worldwide [8, 9].

Based on this experience and lacking national evidence, we initiated a Pilot Program for Primary Prevention of Diabetes of Buenos Aires Province (PPDBA), aiming at evaluating the effectiveness of healthy-lifestyle adoption on the clinical manifestations of T2D in people with PreD. This implementation was preluded by an intense awareness campaign addressed to physicians and other health-care-team members at the primary care level [10, 11] to promote the prevention of the characteristic cardiovascular events [12].

In this case, we attempted to evaluate and report the results of our recruitment procedure of people at risk of developing diabetes in our environment, with currently available tests. We also discussed whether to consider PreD a pre-disease or a fully-fledged one. Thus, we currently described the clinical and biochemical characteristics of people with PreD in the population recruited for the PPDBA study, assuming that publication of this real-world evidence reflecting what health teams are facing in their daily practice will promote a more proactive attitude towards diagnosis and treatment of PreD.

Methods

Information regarding details of the PPDBA study were previously reported [10, 11]. Briefly, it was a prospective, randomized cohort study evaluating the effects of adopting healthy-lifestyles (healthy meal plans and regular practice of physical activity) on the transition from PreD to T2D.

The study recruited men and women between 45 and 75 years of age with PreD, according to American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) criteria [6] in 3 municipalities of Buenos Aires Province (La Plata, Berisso, and Ensenada).

People were recruited using an opportunistic approach: when they visited their physician's office (in public health, social security, and private practices to ensure a wide spectrum of socioeconomic conditions), for reasons other than prediabetes/diabetes, filled out the FINDRISC questionnaire [13]. People with a FINDRISC score ≥ 13 points (cut-off value indicated by Prof Jakko Tuomilheto, a PPDBA advisor) were invited to participate in the study and undergo a free oral glucose tolerance test (OGTT) following WHO recommendations [14]. After informed consent was accepted and signed, we also measured a fasting blood sample for concentrations of HbA1c (by high-performance liquid chromatography technique), creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglyceride by commercial kits. All blood samples were processed in a single laboratory (CentraLab, CABA, Argentina) within 24 h of extraction.

Complementarily, the physician completed a clinical form (QUALIDIAB) that includes clinical and metabolic indicators, self-reported history of CVD, smoking, and use of statins and anti-hypertensive drugs [15]. Body weight was determined with subjects wearing light clothing and no shoes. Height was also measured without shoes, using a metallic metric tape. Body mass index (BMI) was calculated using the formula weight (Kg)/height $(M)^2$. Final BMI data were classified according to the WHO definition into three groups: Normal weight ($18.5 \leq BMI < 25$), Overweight ($25 \leq BMI < 30$) and Obese ($BMI \geq 30$). Waist circumference was measured with a relaxed abdomen using a metallic metric tape on a horizontal plane above the iliac crest. Blood pressure was defined as an average of three measurements taken using a validated oscillometer automatic blood pressure device (OMRON HEM 705 CP) with cuff and bladder dimensions depending on arm circumference [16]. Previously published cut-off points of plasma TG/HDL-C ratios of 2.5 and 3.5 (both expressed in mg/dL) [17], for women and men, respectively, were used to identify participants with insulin resistance (IR). Outcome measurement included attainment of goals defined as waist circumference (Male: ≤102 cm; Female: ≤88 cm), LDL cholesterol ≤100 mg/dl, and Triglyceride <150 mg/dl.

Depending on the OGTT results people with normal glucose tolerance (NGT) were advised to repeat the OGTT in 1 year, whereas those with diagnosis of T2D were referred to their own physician for appropriate treatment. Those who presented PreD were randomly assigned to one of our 2 study groups (intensified and self-administered intervention) as previously reported [10, 11].

Data analysis

FINDRISC score, clinical and laboratory data collected during the recruitment period (2014–2016) were loaded

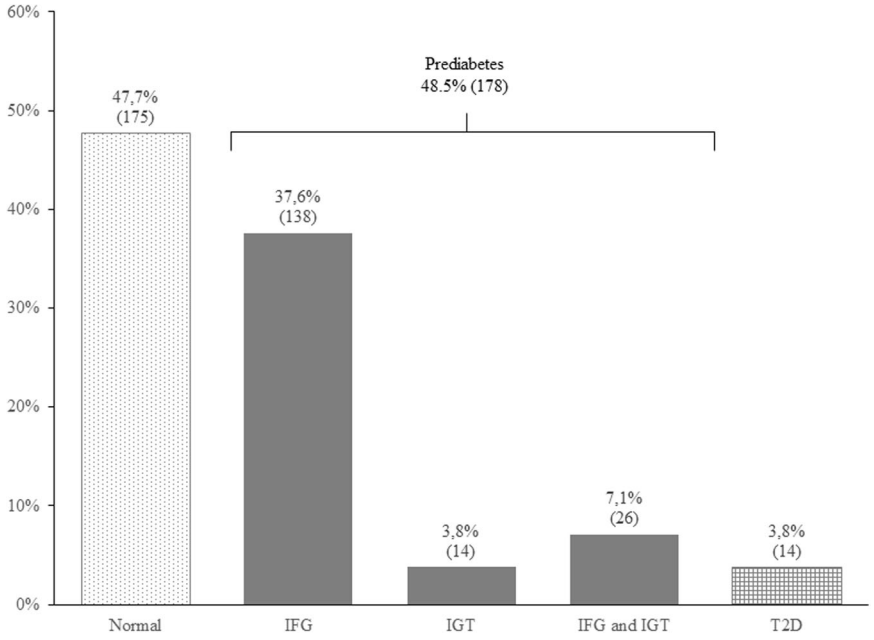

Fig. 1 Results of the Oral Glucose Tolerance Test (OGTT) ($N = 367$). Between parentheses number of cases; IFG impaired fasting glucose, IGT impaired glucose tolerance, T2D type 2 diabete

and stored in a database for subsequent analysis. For this study, no sample size was estimated a priori since all patients who met the PPDBA selection criteria were included. According to OGTT results the sample was divided into NGT (FPG < 100 mg/dL and 2 h post glucose load <140 m/dL) or having PreD, using American Diabetes Association criteria [6]. People who met criteria of diabetes were excluded.

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences), version 15.0 for Windows (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as means and standard deviations (SD) and categorical variables as proportions. Comparisons between NGT and PreD groups were assessed by parametric and nonparametric tests according to the data distribution profile (Kolmogorov-Smirnoff test) for continuous variables or using the $\chi 2$ test to evaluate differences in proportions. Differences with p values <0.05 were considered significant. A logistic regression analysis was run to identify clinical and biochemical characteristics associated with PreD. Potential predictive factors included gender, age, BMI, waist circumference, blood pressure, lipid profile (Total Cholesterol, LDL Cholesterol, and Triglyceride), TG/HDL-C ratios, and outcome measurement as waist circumference, LDL-c and Triglyceride on target. A stepwise selection procedure identified predictive factors significant at 5%.

Ethical statement

The study protocol was evaluated and approved by the Bioethical Committee of the National University of La Plata and the Central Ethics Committee of the Ministry of Health of the Province of Buenos Aires. The study was developed according to the Good Practice Recommendations (International Harmonization Conference) and the ethical guidelines of the Helsinki Declaration. All subjects gave their written informed consent to participate in the study; it was signed before blood samples were collected and the clinical form completed.

Results

From the 367 persons recruited and according to the results of the OGTT, 47.7% of the people have NGT, 48.5% PreD and 3.8% of them had unknown/undiagnosed and consequently untreated T2D (Fig. 1). People with TD2 were excluded from our study; thus, the final number of people used for statistical analysis was 353: 175 NGT and 178 PreD. The later group included 90% of people with IFG, 7,9% with IGT and 14.6% with both impairments.

FINDRISC score showed no significant differences between groups (16.9 ± 1.9 vs. 17.2 ± 2.2, $p = 0.106$). People with PreD were significantly older, had a significantly higher percentage of overweight/obesity, higher BMI, and larger waist circumference than NGT (Table 1).

Their biochemical profile showed significantly higher values of fasting and 2 h post glucose load, HbA1c values, and triglyceride. No significant differences were recorded in the lipid profile though both groups had high abnormal LDL-c values.

The percentage of people having triglyceride/HDL-cholesterol ratios above the cut off values for our

Table 1 Metabolic characteristics of the cohort

Parameter	NGT ($N = 175$)		PreD ($N = 178$)		p
	Value	n	Value	n	
Female	64.0%	112	57.9%	103	0.238
Age (years)	56.0 ± 7.5	175	58.6 ± 7.7	178	0.001
FINDRISC score	16.9 ± 1.9	175	17.2 ± 2.2	178	0.106
BMI (kg/m^2)	31.1 ± 5.9	169	32.7 ± 5.6	167	0.013
Normal Weight	14.8%	25	4.8%	8	0.006
Overweight	29.6%	50	28.7%	48	
Obesity	55.6%	94	66.5%	111	
Waist (cm)	101.5 ± 15.3	167	105.9 ± 15.3	165	0.018
Waist circumference (≤Male: 102 cm; Female: 88 cm)	27.5%	46	20.6%	34	0.139
Fasting Glucose (mg/dL)	92.3 ± 8.7	175	109.1 ± 7.7	178	0.000
Postprandial Glucose (mg/dL)	83.2 ± 22.5	175	110.6 ± 34.5	178	0.000
HbA1c (%)	5.5 ± 0.4	170	5.8 ± 0.4	174	0.000
HbA1c (mmol/mol)	37 ± 2.7	170	40 ± 2.7	174	0.000
SBP (mmHg)	135.4 ± 16.7	171	138.1 ± 16.2	176	0.118
DBP (mmHg)	83.1 ± 10.5	171	83.4 ± 9.3	176	0.470
Total cholesterol (mg/dL)	200.8 ± 40.0	168	200.1 ± 41.1	171	0.869
LDL-cholesterol (mg/dL)	123.9 ± 34.2	167	119.6 ± 34.9	167	0.267
HDL-cholesterol (mg/dL)	49.9 ± 10.8	168	50.0 ± 14.7	171	0.427
Triglyceride (mg/dL)	135.5 ± 66.9	168	155.4 ±	171	0.009
Triglyceride on target (%)	69.0%	116	57.3%	98	0.025
TG/ HDL-c ratio	3.0 ± 1.9	168	3.5 ±	171	0.015
High TG/HDL-c ratio (IR indicator)	37.5%	63	55.0%	94	0.001

Mean ± Standard deviation

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TG* triglyceride, *IR* insulin resistance

Table 2 Clinical background, therapeutic characteristics and family history of the cohort according to OGTT result ($N = 353$)

Parameter	NGT ($n = 175$)	PreD ($n = 178$)	p
Clinical background			
Hypertension	92.6%	75.3%	0.000
Dyslipidemia	17.7%	29.8%	0.008
Obesity	6.3%	17.4%	0.001
Cardiovascular disease	6.6%	10.6%	0.190
Chronic obstructive pulmonary disease (COPD)	4.2%	7.1%	0.254
Asthma	3.0%	7.1%	0.088
Hypothyroidism	4.2%	10.0%	0.038
Therapeutic characteristics			
ASA use (%)	20.6%	14.6%	0.141
Antihypertensive drugs use (%)	58.9%	63.5%	0.373
Statins drugs use (%)	18.3%	23.6%	0.220
Family history			
AMI	5.1%	14.0%	0.007
Diabetes	70.2%	62.7%	0.144
Hypertension	86.9%	75.2%	0.006
Dyslipidemia	49.4%	42.4%	0.218
Cardiovascular disease	7.9%	17.8%	0.011

NGT normal, *PreD* prediabetes, *ASA* acetylsalicylic acid, *AMI* acute myocardial infarction

Table 3 Logistic regression analysis

Variable	B	SE	OR	95% CI for OR	
Age (years)	0.057	0.016	1.058	1.026	1.091
Waist (cm)	0.018	0.008	1.018	1.001	1.035
Triglycerides on target (TG < 150 mg/dl)					
No	Referent				
Yes	−0.534	0.249	0.586	0.360	0.954
Intercept	−4.802	1.306	0.008		

SE standard error, *OR* odds ratio, *CI* confidence interval, *TG* triglyceride

population [17] was significantly larger in people with PreD (55% vs. 37.5%).

The clinical records of people with PreD exhibited a significantly higher background percentage of dyslipidemia, obesity, and hypothyroidism (Table 2). No significant differences among groups were recorded in the antihypertensive and statins drugs used, although higher values were recorded for cardiovascular disease (17.8%. vs. 7.9%).

Logistic regression analysis showed that PreD was significant and independently associated with age (OR, 1.058; 95% CI, 1.026 to 1.091), waist circumference (OR, 1.018; 95% CI, 1.001 to 1.035) and triglyceride on target (OR, 0.586; 95% CI, 0.360 to 0.954) (Table 3).

Discussion

Prediabetes represents a large percentage of the population with dysglycemia, portraying a high risk of developing T2D within a relatively short period [6, 7]. This dysfunction is predictable but is not immediately demonstrated by FINDRISC. For this reason, its metabolic dysfunction is not diagnosed in these terms, and consequently not properly and efficiently prevented [13].

Meantime, it has been proved that different types of dysglucemia (IFG, IGT and their combination) have significant different yearly-conversion-rates of PreD to

diabetes ranging from 3 to 12 years [7], and therefore we also need to identify their proper status by a complementary procedure (OGTT).

Considering that IFG has already shown a 50% decrease of B-cell population [18], PreD is also associated with either micro- [19] or macro-angiopathic lesions—as recently reported in these population by our group [20]—and with consecutive cumulative diagnostic delayed cardiovascular events [7], its non-detection and properly treated represents a heavy but preventable economic burden. However, despite the strong previously reported evidences plus the current ones, PreD is not properly considered for early diagnosis and appropriate treatment, particularly at the primary care level.

The recently successful reversible obese-T2D induced at primary care level in patients with less than 5 years of diabetes duration, adds additional support/pressure to the importance of early diagnosis of the disease. In fact, any delay decreases the possibilities of endogenous B-cell recovery (2-year results of the DIRECT open-label, cluster-randomised trial) [21].

In our population, people with PreD were older compared to normal ones, had larger BMI, waist circumference and triglyceride levels, as well as a high TG/HDL-c ratio, a well-known signs of insulin resistance. This association shows the frequent presence of metabolic syndrome in these people [20, 22, 23]. Simultaneously, they had abnormally high HbA1c levels, fasting and/or postprandial dysglycemia, or both, and more frequent antecedents of dyslipidemia, cardiovascular disease and other pathologies such as hypothyroidism. The later was reported by our group [24] as well as the frequent associations with waist circumference [11]. Altogether, these characteristics potentiate the patient's cardiovascular risk and add complexity to their metabolic dysfuction [25, 26].

As shown in our regression analysis -for the first time- older age and larger waist circumference increased the probability that the person had PreD, whereas having triglyceride values on target (TG < 150 mg/dl) was a protective factor.

A significant delay in pulse-wave as recently reported by our group [20], and cardiovascular lesions [27], build up a constellation of serious dysfunctions shown by different authors, provide a strong support to consider the PreD syndrome as a serious dysfunction. By adopting this attitude, physicians may provide an active preventive role in decreasing the cumulative incidence of cardiovascular events due to PreD/diabetes [28].

In other words, our current data together with their close concordance with other evidence arising from clinical and biochemical indicators obtained from different ethnics, socioeconomic populations and researchers, lend strong support to our conclusions: i.e. we can decrease the PreD/diabetes-diagnosis-elapsed time until effective treatment prescription, thereby decelerating its incessant worldwide progression, through earlier identification of the disease's real pathogeny.

There is no doubt that diabetes prevention requires a combined strategy of early diagnostic attitude, thereby providing the opportunity for treatment success, and the decision to act together with individual and the public health authorities' power, to deal with the problem. By adopting this behavior in time, we can certainly beat the hard battle against diabetes.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval The study protocol was evaluated and approved by the Bioethical Committee of the National University of La Plata and the Central Ethics Committee of the Ministry of Health of the Province of Buenos Aires. The study was developed according to the Good Practice Recommendations (International Harmonization Conference) and the ethical guidelines of the Helsinki Declaration.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Instituto Nacional de Estadísticas y Censos (INDEC). Resultados de la 4ta. Encuestan Nacional de Factores de Riesgo. Available online: http://www.msal.gob.ar/images/stories/bes/graficos/0000001622cnt-2019-10_4ta-encuesta-nacional-factores-riesgo.pdf (accessed on June 6th, 2020)
2. A. Morsanutto, P. Berto, S. Lopatriello et al. Major complications have an impact on total annual medical costs of diabetes: results of a database analysis. J. Diabetes Complications **20**, 163–169 (2006). https://doi.org/10.1016/j.jdiacomp.2005.06.011
3. J.F. Elgart, S. Asteazarán, J.L. De La Fuente et al. Direct and indirect costs associated to type 2 diabetes and its complications measured in a social security institution of Argentina. Int. J. Public Health **59**(5), 851–857 (2014). https://doi.org/10.1007/s00038-014-0604-4
4. R.A. DeFronzo, Pathogenesis of type 2 diabetes mellitus. Med. Clin. North Am. **88**, 787–835 (2004). https://doi.org/10.1016/j.mcna.2004.04.013

5. M. Prestes, M.A. Gayarre, J.F. Elgart et al. Improving diabetes care at primary care level with a multistrategic approach: results of the DIAPREM Programme. Acta Diabetol. **54**(9), 853–861 (2017). https://doi.org/10.1007/s00592-017-1016-8
6. S.E. Inzucchi, R.M. Bergenstal, J.B. Buse et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care **35**(6), 1364–1379 (2012). https://doi.org/10.2337/dc12-0413
7. H.C. Gerstein, P. Santaguida, P. Raina et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin. Pr. **78**(3), 305–312 (2007). https://doi.org/10.1016/j.diabres.2007.05.004
8. A. Zand, K. Ibrahim, B. Patham, Prediabetes: why should we care? Methodist Debakey Cardiovasc J. **14**(4), 289–297 (2018). https://doi.org/10.14797/mdcj-14-4-289
9. G.A. Nichols, H.S. Glauber, J.B. Brown, Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. Diabetes Care **23**, 1654–1659 (2000)
10. J.J. Gagliardino, G. Etchegoyen, M. Bourgeois et al. Prevención primaria de diabetes tipo 2 en Argentina: estudio piloto en la provincia de Buenos Aires. Rev. Argent. Endocrinol. Metab. **53**, 135–141 (2016)
11. Gagliardino J.J., Elgart J.F., Bourgeois M., et al. (2018) Diabetes primary prevention program: new insights from data analysis of recruitment period. Diabetes Metab. Res. Rev. 34(1) https://doi.org/10.1002/dmrr.2943
12. Y. Huang, X. Cai, W. Mai, M. Li, Y. Hu, Association between prediabetes and risk of cardiovascular disease and all-cause mortality: systematic review and meta-analysis. BMJ **355**, i5953–i5964 (2016)
13. T. Saaristo, M. Peltonen, J. Lindstrom et al. Cross-sectional evaluation of the Finnish Diabetes Risk Score: a tool to identify undetected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome. Diab. Vasc. Dis. Res. **2**(2), 67–72 (2005). https://doi.org/10.3132/dvdr.2005.011
14. WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: World Health Organisation; 1999. Report No 99.2.11
15. J.J. Gagliardino, M. de la Hera, F. Siri; Grupo de Investigación de la Red QUALIDIAB, Evaluation of the quality of care for diabetic patients in Latin America. Rev. Panam. Salud Publica **10**(5), 309–317 (2001)
16. B. Williams, G. Mancia, W. Spiering et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur. Heart J. **39**(33), 3021–3104 (2018). https://doi.org/10.1093/eurheartj/ehy339
17. M.R. Salazar, H.A. Carbajal, W.G. Espeche et al. Relation among the plasma triglyceride/high-density lipoprotein cholesterol concentration ratio, insulin resistance, and associated cardio-metabolic risk factors in men and women. Am. J. Cardiol. **109**(12), 1749–1753 (2012). https://doi.org/10.1016/j.amjcard.2012.02.016
18. A.E. Butler, J. Janson, S. Bonner-Weir, R. Ritzel, R.A. Rizza, P.C. Butler, Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes **52**(1), 102–110 (2003)
19. S.R. Patel, S. Bellary, L. Qin et al. Abnormal retinal vascular reactivity in individuals with impaired glucose tolerance: a preliminary study. Invest Ophthalmol. Vis. Sci. **53**(9), 5102–5108 (2012). https://doi.org/10.1167/iovs.12-9512
20. J.J. Gagliardino, M.R. Salazar, W.G. Espeche et al. Arterial stiffness: its relation with prediabetes and metabolic syndrome and possible pathogenesis. J. Clin. Med. **10**(15), 3251 (2021). https://doi.org/10.3390/jcm10153251
21. M.E.J. Lean, W.S. Leslie, A.C. Barnes et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. **7**(5), 344–355 (2019). https://doi.org/10.1016/S2213-8587(19)30068-3
22. S.M. Williams, A. Eleftheriadou, A. Alam, D.J. Cuthbertson, J.P.H. Wilding, Cardiac autonomic neuropathy in obesity, the metabolic syndrome and prediabetes: a narrative review. Diabetes Ther. **10**, 1995–2021 (2019). https://doi.org/10.1007/s13300-019-00693-0
23. R. Meamar, M. Amini, A. Aminorroaya, M. Nasri, M. Abyar, A. Feizi, Severity of the metabolic syndrome as a predictor of prediabetes and type 2 diabetes in first degree relatives of type 2 diabetic patients: a 15-year prospective cohort study. World J. Diabetes **11**(5), 202–212 (2020). https://doi.org/10.4239/wjd.v11.i5.202
24. A.M. Cortizo, G.D. Chazenbalk, E.E. de Gagliardino et al. Thyroid hormone binding and deiodination by pancreatic islets: relationship with the in vitro effect upon insulin secretion. Acta Endocrinol. (Copenh) **116**(1), 66–72 (1987)
25. K.A. Young, C.H.G. Scott, R.J. Rodeheffer, H.H. Chen, Incidence of preclinical heart failure in a community population. J. Am. Heart Assoc. **11**(15), e025519 (2022). https://doi.org/10.1161/JAHA.122.025519
26. N. Gronich, S.N. Deftereos, I. Lavi et al. Hypothyroidism is a risk factor for new-onset diabetes: a cohort study. Diabetes Care **38**(9), 1657–1664 (2015). https://doi.org/10.2337/dc14-2515
27. Y. Zhao, M. Guo, G. Shi, Prediabetes predicts adverse cardiovascular outcomes after percutaneous coronary intervention: a meta-analysis. Biosci. Rep. **40**(1), BSR20193130 (2020). https://doi.org/10.1042/BSR20193130
28. W.H. Herman, W. Ye, S.J. Griffin et al. Early detection and treatment of type 2 diabetes reduce cardiovascular morbidity and mortality: a simulation of the results of the Anglo-Danish-Dutch Study of intensive treatment in people with screen-detected diabetes in primary care (ADDITION-Europe. Diabetes Care 38(8), 1449–1455 (2015). https://doi.org/10.2337/dc14-2459