DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2015; **31**: 368–375.
Published online 12 December 2014 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/dmrr.2618

RESEARCH ARTICLE

Dysglycemia and long-term mortality: observations from the Israel study of glucose intolerance, obesity and hypertension

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Received: 22 July 2014
Revised: 7 October 2014
Accepted: 11 October 2014

Abstract

Background We describe the relationship between dysglycemia and long-term mortality and elucidate the relationship between blood glucose levels during an oral glucose tolerance test (OGTT) and haemoglobin A1 (HbA1) and mortality.

Methods A cohort of 1410 individuals was followed for 33 years since 1980. Fasting and post-OGTT glucose parameters were used to categorize the cohort according to baseline glycemic status.

Results The mortality rate increased from 43% in normoglycemic individuals to 53.3, 61.7, 72.9 and 88.0% in those with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG/IGT and diabetes, respectively. The highest mortality rate, compared with the normoglycemic category, was observed in individuals with IFG/IGT and diabetes according to a Cox proportional hazard model (HR = 1.38, 95%CI 1.10–1.74 and HR = 2.14, 95%CI 1.70–2.70, respectively), followed by individuals with IGT and IFG, but this did not reach statistical significance. We speculate that the IFG group may represent a mixture of individuals en route from normal to the next two categories as well as another cohort whose glucose levels are stably set at the upper reaches of the normal distribution.
Significant differences were found between 1 and 2 h glucose values ($p < 0.001$). Fasting, 60 and 120 min glucose values were positively associated with increasing HbA1 quintiles ($p < 0.05$). The mean HbA1 was significantly higher in those who died ($p = 0.01$). The highest mortality (58.8%) was observed in the upper HbA1 quintile that was also associated with the highest prevalence of the metabolic syndrome (17.2%).

Conclusions This study shows a continuous relationship between the severity of dysglycemia and long-term mortality and should promote the early recognition of prediabetes. The 1 h post-load glucose level was continuously associated with increasing HbA1 concentrations and may therefore serve as an early marker for abnormalities in glucose tolerance. An elevated 1 h post-load glucose level may potentially identify at-risk individuals well before the traditional 2 h glucose value. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords dysglycemia; HbA_{1c}; mortality; OGTT; prediabetes; prevention; metabolic syndrome

Introduction

Prediabetes, comprising impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is frequently undetected and associated with an increased risk for the development of diabetes and cardiovascular disease (CVD) [1]. The highest risk for diabetes and associated cardiovascular risk factors occurs in those with combined IFG and IGT [1]. Threshold levels for dysglycemic states are defined by absolute fasting plasma glucose (FPG), a 2 h glucose value during an oral glucose tolerance test (OGTT) or glycohemoglobin (Hb1Ac) criteria. An International Expert Committee (IEC) in 2009 recommended that a haemoglobin A1c (HbA_{1c}) threshold of 6.5% (48 mmol/mol) could also be used for diagnosing diabetes, a position adopted by both the American Diabetes Association (ADA) and the World Health Organization (WHO) [2]. Furthermore, the diagnosis of prediabetes, defined by a HbA_{1c} value between 5.7 and 6.4% (39–46 mmol/mol), was accepted by the ADA but not WHO. The IEC defined a lower risk category for developing type 2 diabetes in those with a $HbA_{1c} \geq 5.7$–5.9% (39–41 mmol/mol) and a higher risk category in those with $HbA_{1c} \geq 6.0$–6.4% (42–46 mmol/mol). The use of HbA_{1c} for screening and diagnosing dyglycemic states has recently been reviewed and remains controversial [3,4].

The current study is based on longitudinal data from the Israel Study of Glucose Intolerance, Obesity and Hypertension (The Israel GOH Study). In the 1980s, it was accepted that although HbA_{1c} correlated best with the average blood glucose concentration over preceding months, for clinical purposes, however, the measurement of total HbA1 could be substituted. HbA1 represents the total glycated haemoglobin and is composed of several fractions designated HbA1a through HbA1e of which HbA_{1c} is the major component [5]. The aim of this study is to describe the relationship between metabolic biomarkers and HbA1 and to elucidate the association between HbA1 and long-term mortality. Specifically, we compared HbA1, metabolic variables and total mortality during a 33 year follow-up in 1410 individuals with normoglycemia (NGT), IFG, IGT and diabetes.

Materials and methods

Study population

This report is a follow-up of the The Israel GOH Study. In 1967 (designated as the first phase of the study), a population sample was randomly drawn from the Israel Central Population Registry [6–8] that was stratified according to sex (50% male and female), age (33% from each 10 year increment of subjects born between 1912 and 1941) and four ethnic groups (European–American origin, North African, Yemenite and other Middle Eastern). European origin represents individuals born in Europe or whose ancestors came from Europe either directly or through America. A deliberate increase in the sampling fraction of the Yemenite-born group was undertaken in order to enable a balanced evaluation of morbidity and mortality.

The sampling procedure and design of the GOH study are detailed elsewhere [6–8]. From 1979 to 1984, referred to as baseline, 2769 subjects completed an OGTT of whom 1410 had HbA1 measurements. Insulin and HbA1 measurements were added to the study protocol later in the data collection phase and therefore are available for only a subsample of the 2769 participants with OGTT. No major differences in the age-sex-ethnic origin distributions of the study group compared with the original cohort were noted. A flow chart of survival, inclusion and follow-up for the current report is illustrated in Figure 1. All subjects were home interviewed, and their weight, height and blood pressure were measured by trained nurses. Four blood pressure measurements were taken by mercury sphygmomanometer in the sitting position in the left arm, twice before and after the interview. At this phase, laboratory tests (fasting glucose, fasting insulin, HbA1) and a 2 h 100 g OGTT were performed. Linkage of the study file with the National Population Registry, updated till December 2012, by a unique identification number assigned to each Israeli citizen, enabled a complete survival status assessment.

Laboratory tests

Glucose: A 100 g oral glucose load was used instead of the standard 75 g because the former has little effect on glucose levels [9] but enhances insulin response [10]. Plasma glucose and insulin levels were determined 1 and 2 h after the glucose load. The facilities of Sheba Medical Center were used for laboratory examinations. Plasma glucose was determined by an automated Technicon Autoanalyzer II method (Technicon Instruments Corp., Tarrytown, NY), using potassium ferrocyanide reduction.

Insulin: Plasma insulin was determined, according to the laboratory assays available at the time, in duplicate by the Phadebas Radioimmunoassay kit (Pharmacia Diagnostics Inc., Piscataway, NJ), the within-assay coefficient of variation being 4% and the between-assay coefficient 8% [11].

HbA1: HbA1 was determined as % of total haemoglobin by a commercial minicolumn method (Helena Laboratory (Beaumont, TX) Minicolumn kits were chosen to facilitate population screening. The within-assay coefficient of variation based on 30

DOI: 10.1002/dmrr

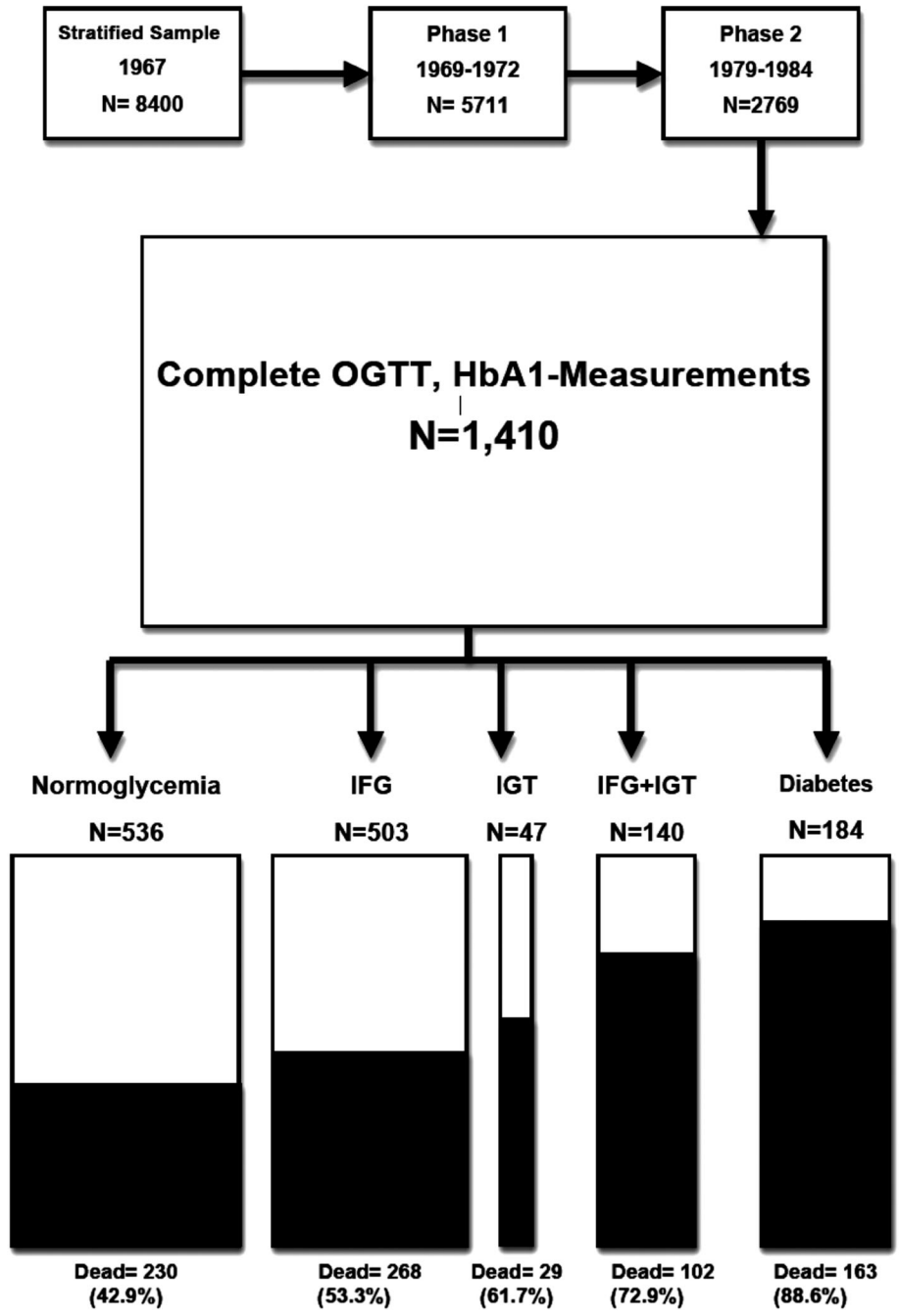

Figure 1. Study cohort

replicates ranged from 3% in the lower concentration range (HbA1 < 6.0%) to 6% in the higher range (HbA1 ≥ 8.0).

Definitions

IFG was defined as a FPG ≥ 100 mg/dL (5.6 mmol/L) and < 126 mg/dL (7.0 mmol/L) and a 2 h post-load glucose < 140 mg/dL (7.8 mmol/L). IGT was defined as 2 h post-load glucose ≥ 140 mg/dL (7.8 mmol/L) and < 200 mg/dL (11.1 mmol/L). IFG/IGT was defined as individuals who fulfilled definitions of both IFG and IGT. Because of the small number of individuals with IGT ($n = 47$), we combined this group with the IFG/IGT group for subsequent analysis. Type 2 diabetes was defined by a FPG ≥ 126 mg/dL (7.0 mmol/L) and/or 2 h glucose ≥ 200 mg/dL (11.1 mmol/L). HOMA1-%B = (20 × FPI) /

DOI: 10.1002/dmrr

(FPG × 0.05551 − 3.5), where FPI is fasting plasma insulin (mU/L) and FPG expressed as (mg/dl). HOMA1-IR = (FPI × FPG × 0.05551) / 22.5. The metabolic syndrome was defined by ATP III criteria, substituting the waist circumference criteria with a BMI ≥ 30 kg/m^2 [12].

Statistical analysis

Associations between participants demographic (age and sex), smoking and health baseline characteristics (BMI, blood pressure and glycemic status) according to survival status were tested using the chi-square test or Fisher's exact test for categorical variables. For continuous variables, differences by survival status were examined through student *t*-test, and one-way analysis of variance was performed for differences between the three groups of glycemic status. Spearman correlation test was used to evaluate associations between the mean plasma values and HbA1 levels. Mortality follow-up was performed by the end of 2012. Cox proportional hazard model was used to study variables that were significantly and independently associated with mortality. To test the proportional hazard assumption, we generated time-dependent covariates by creating interaction terms for the independent variables and time and included them in the model. The assumption of proportionality was not found to be statistically significant ($p = 0.25$). All analyses were two-tailed and performed using SAS (version 9.2).

Results

The study sample from the Israel GOH cohort comprised 736 (52.2%) males and 674 (47.8%) females. The mean age at baseline was 53.1 ± 8.0 years ranging from 39 to 68 years. 40% of the cohort reported current or past smoking (Table 1). Study subjects were distributed according to five glycemic groups: 536 (36.0%) with NGT, 503 (35.7%) as IFG, 47 (3.3%) as IGT alone, 140 (9.9%) having both IFG and IGT and 184 (13.1%) having diabetes. As can be seen in Table 1, baseline characteristics of the study cohort, aside from ethnic origin, differed significantly according to follow-up survival status. The mean age at baseline was 8 years older in those who died than those who survived.

Of the 1410 individuals, 791 (56.1%) died, with a higher mortality rate among men than women (62.6 vs 49.0%) and among smokers than non-smokers (60.0 vs 53.5%). The mortality rate increased according to metabolic status: 43% in those with NGT and 53.3, 61.7, 72.9 and 88.0% in those with IFG, IGT, IFG/IGT and diabetes, respectively (Figure 1). The mean HbA1 was significantly higher in those who died than those who survived

Table 1. Baseline characteristics of the study sample by vital status

	Total, *N* = 1410	Died, *N* = 791	Alive, *N* = 619	*p*, deceased *versus* living
Sex				
Men	736 (52.2)	461 (58.3)	275 (44.4)	<0.001
Women	674 (47.8)	330 (41.7)	344 (55.6)	
Age (years)	53.1 ± 8.0	56.9 ± 7.1	48.2 ± 6.3	<0.001
Ethnic origin				
Europe/America	462 (32.8)	260 (32.9)	202 (32.7)	0.55
Middle East	356 (25.3)	190 (24.0)	166 (26.9)	
North Africa	281 (19.9)	166 (21.0)	115 (18.6)	
Yemen	310 (22.0)	175 (22.1)	135 (21.8)	
BMI (kg/m^2)				
Men	25.7 ± 3.5	25.8 ± 3.6	25.4 ± 3.3	0.16
Women	26.6 ± 4.8	27.8 ± 5.4	25.5 ± 4.0	<0.001
Blood pressure (mmHg)				
Systolic	135.1 ± 22.4	142.4 ± 23.2	125.7 ± 17.1	<0.001
Diastolic	86.1 ± 11.6	88.5 ± 12.1	83.1 ± 10.1	<0.001
Smoking				
Current or past	560 (39.7)	336 (42.5)	224 (36.2)	0.02
Never	850 (60.3)	455 (57.5)	395 (63.8)	
Glucose metabolic state				
Normoglycemic	536 (36.0)	230 (29.1)	306 (49.4)	<0.001
IFG	503 (35.7)	268 (33.9)	235 (38.0)	
IGT	47 (3.3)	29 (3.7)	18 (2.9)	
IFG + IGT	140 (9.9)	102 (12.9)	38 (6.1)	
Diabetic	184 (13.1)	162 (20.5)	22 (3.6)	
HbA1 % (mean ± SD)	7.07 ± 1.21	7.24 ± 1.30	6.87 ± 1.04	<0.001
Insulin fasting (mU/L)	15.7 ± 10.8	16.5 ± 12.1	14.5 ± 8.9	<0.001

DOI: 10.1002/dmrr

Table 2. Glycemic biomarkers of the 1226 non-diabetic individuals of the cohort according to glycemic status

	Normoglycemic	IFG	IGT (and IFG)	
	N = 536	*N* = 503	*N* = 187	Overall *p**
FPG (mg/dL)	89.4 ± 6.6	105.0 ± 6.2	103.3 ± 9.5	<0.001
GT 1 h (mg/dL)	120.8 ± 34.8	145.3 ± 38.6	184.9 ± 40.8	<0.001
GT 2 h (mg/dL)	99.7 ± 16.8	109.4 ± 15.9	158.5 ± 14.8	<0.001
HbA1 (%)	6.70 ± 1.05	7.03 ± 1.00	7.18 ± 1.04	<0.001
Fast insulin (mU/L)	13.3 ± 8.0	15.2 ± 8.9	16.3 ± 10.5	<0.001
1 h insulin (mU/L)	69.5 ± 46.5	85.6 ± 50.3	95.3 ± 55.1	<0.001
2 h insulin (mU/L)	57.8 ± 40.3	68.8 ± 43.1	112.6 ± 59.2	<0.001
HOMA-IR	2.95 ± 1.84	3.9 ± 2.3	4.17 ± 2.8	<0.001
HOMA-b	50.3 ± 31.7	48.8 ± 30.9	53.5 ± 36.6	0.25

*All comparisons were highly statistically significant after Bonferroni correction for multiple comparisons ($p < 0.05$) except for the following differences between IFG and IFG/IGT: fast insulin, 1 and 2 h insulin and HOMAs and between IGT/IFG and normoglycemics for 30 min insulin. HOMA-b was not statistically significant as well.
To convert mg/dL to mmol/L divide by 18 or multiply by 0.05551.

throughout the follow-up period ($p = 0.01$). Further analysis combined the IGT with the IFG/IGT groups.

Table 2 presents mean values ± SD of glucose and insulin during the OGTT test by glycemic groups of the 1226 subjects without diabetes. All glycemic parameters including HbA1 were significantly different among the three glycemic groups ($p < 0.001$) except for HOMA-b. In addition, expected significant differences were found between the 1 and 2 h glucose values ($p < 0.001$, not shown).

Mean plasma values for biomarkers according to HbA1 quintiles of the non-diabetic subjects are shown in the appendix. Fasting, 60 and 120 min glucose values during the OGTT were positively associated with increasing HbA1 quintiles ($p < 0.05$) as were fasting insulin and HOMA-IR ($p = 0.03$ and 0.003, respectively). BMI, blood pressure, total cholesterol, triglycerides and HOMA-β were not statistically significantly associated with HbA1 quintiles, while 1 h insulin had borderline significance ($p = 0.07$). The HDL cholesterol was significantly associated with HbA1 values reaching statistical significance in men only. The upper HbA1 quintile (Q5) was associated with a greater proportion of individuals having the metabolic syndrome compared with the lower quintiles (17.7 vs 12.7%, $p = 0.059$, not shown). The highest mortality rate (58.8%) was also observed in the upper HbA1 quintile (Q5). These results persisted when HbA1 was examined as a continuous variable according to the Spearman correlation test (not shown).

In Cox proportional hazard models, the crude first model (not shown) demonstrated a highly significant association between the upper quintile of HbA1 compared with the lower four quintiles and time to death (HR = 1.47, 95%CI: 1.25–1.71). This statistically significant association persisted when adjusting for sex, age, smoking, BMI and blood pressure (HR for HbA1 Q5 vs Q1–4 = 1.27, 95%CI 1.08–1.49) but became non-statistically significant when further adjusting for glycemic group.

Table 3 presents the factors found to associate over time with death resulting from the adjusted Cox proportional hazard model. Individuals with HbA1 in the upper quintile (Q5) had a 13% greater risk for mortality than those in quintiles 1–4 although not reaching statistical significance when adjusted for age, sex, smoking, BMI, blood pressure and glycemic group ($p = 0.16$). Women had a 29% lower risk for death than men ($p < 0.001$). Older age, systolic blood pressure and history of smoking increased the risk for death. Individuals with IFG/IGT

Table 3. Cox proportional hazard model for factors associated with mortality

Characteristic	Reference category	HR	95%CI	*p*
HbA1 (quintile 5)	Q1–Q4	1.13	0.95–1.33	0.16
Sex (female)	Male	0.71	0.60–0.83	<0.001
Age (years)	1 year increment	1.10	1.09–1.11	<0.001
Smoking (current/past)	Never	1.14	0.97–1.32	0.1
BMI	1 kg/m^2 increment	1.00	0.98–1.02	0.9
Systolic BP	1 mmHg increment	1.02	1.01–1.03	<0.001
Diastolic BP	1 mmHg increment	0.99	0.98–1.00	0.02
Glycemic group	Normoglycemic			
IFG		1.08	0.90–1.30	0.4
IGT and IGT/IFG		1.38	1.10–1.74	0.005
Diabetic individuals		2.14	1.70–2.70	<0.001

DOI: 10.1002/dmrr

and those with diabetes had a significantly higher risk than those with normoglycemia (HR = 1.38, 95%CI 1.10–1.74; HR = 2.14, 95%CI 1.70–2.70, respectively). IFG alone was not found to increase the risk for death. Fasting insulin was not found to associate with mortality ($p = 0.6$) in the presence of HbA1 and the other factors presented in the model.

Discussion

The present study demonstrates that although both 1 and 2 h post-load glucose levels significantly correlated with higher HbA1 concentrations, the 1 h level was invariably higher across HbA1 quintiles within the non-diabetic range. This observation is consistent with and extends previous findings relating elevations in 1 h post-load levels with progression to prediabetes and diabetes [13–15]. The incremental increase in the 1 h glucose levels may explain the progressive elevation in HbA1 quintiles as the 2 h glucose levels changed minimally. This observation suggests that the standard 2 h OGTT may therefore underestimate the severity of glucose especially at lower HbA1 concentrations.

Elevated 2 h glucose levels, even within the normal range, occur considerably late in the evolution to diabetes [16], thereby delaying an opportunity for earlier diagnosis and intervention. Furthermore, as HbA_{1c}, categorized in the general population according to <5.7, 5.7–6.4 and $\geq 6.5\%$, is insensitive and has poor positive predictive value for diagnosing diabetes compared with the fasting plasma glucose [17]; the 1 h postprandial glucose level may identify those at risk before progression occurs. Therefore, those at risk should therefore preferably be diagnosed with the OGTT [18] as it is more predictive for diagnosing glucose abnormalities than the FPG alone. The early diagnosis of dysglycemic conditions could be facilitated by measuring the 1 h rather than the 2 h post-load glucose level.

In this study, differences between the 1 and 2 h glucose levels were consistently highly significant ($p < 0.001$) in the total group, stratifying by HbA1 quintiles and according to glycemic status. The elevation in the 1 and 2 h glucose levels were significantly higher in individuals with IFG/IGT compared with the IFG group. The 1 h rather than the 2 h glucose levels would identify individuals with IGT within the normoglycemic and IFG groups and those with diabetes in the IFG/IGT group.

The fifth HbA1 quintile, ranging from 7.8 to 11.0%, corresponded to a mean 1 h glucose level of 150.4 mg/dL (8.4 mmol/L), comparable to previous observations [13–15] suggesting that a 1 h value exceeding 155 mg/dL (8.61 mmol/L) increases considerably the risk for developing diabetes.

Insulin concentrations also increased progressively with worsening glycemic status. Fasting insulin levels, while not different between the IFG and IFG/IGT groups, differed significantly from the normoglycemic group. The 1 and 2 h insulin levels in the IFG/IGT group were also significantly higher than in the IFG group. Whereas the 2 h insulin level continued to increase in the IFG/IGT group compared with the 1 h level, the IFG group demonstrated a decline in the 2 h insulin level likely related to the relative absence of peripheral insulin resistance described in this population [19–21].

A highly significant association between the upper quintile of HbA1 compared with the lower four quintiles and time to death was observed that persisted when adjusting for sex but gradually declined when further adjustments were made for age, smoking, BMI and blood pressure. Adjusting for the previous parameters and the glycemic group, the fifth quintile of the HbA1 exhibited a 15% increased HR for mortality compared with the lower four quintiles. In addition, the IGT and IGT/IFG groups conferred a 36% greater mortality risk than the normoglycemic group. The latter observation is consistent with those of Selvin et al. who found that glycated haemoglobin levels, especially at values above 6.0%, were associated with an increased risk of diabetes and CVD and death from any cause compared with fasting glucose [22]. Unwin et al. also observed that HbA_{1c} levels were continuously and positively associated with CVD and total mortality independent of CVD risk factors [1]. A prospective study analysing the risk of CV events associated with HbA_{1c} levels $\geq 5\%$ showed a graded relationship and risk of all-cause mortality, ischemic heart disease mortality and CVD death. For every 1% rise in HbA_{1c}, there was a 41% increase observed in CV mortality [23]. As those in the highest HbA1 quintile were associated with the highest prevalence of the metabolic syndrome, the latter may have also contributed to the increased mortality as the metabolic syndrome has been shown to predict prevalent and incident type 2 diabetes mellitus and cardiovascular disease [12,24].

Individuals with IFG/IGT and diabetes, corresponding to higher HbA1 quintiles, had a significantly higher mortality risk than those with normoglycemia. Isolated IFG was not found to increase the risk for death in line with other studies suggesting that the risk for CVD in prediabetes was better predicted by IGT than IFG [25–28]. We speculate that the IFG group may represent a mixture of individuals en route from normal to the next two categories as well as another cohort whose glucose levels are stably set at the upper reaches of the normal distribution.

Among the strengths of the present study are the long follow-up period of up to 40 years, the relatively large cohort and the random sampling of a representative cohort from the National Population Registry, comprising a diverse migrant population.

DOI: 10.1002/dmrr

Some limitations must be addressed in relation to this study. Principally, HbA_{1c} measurements were substituted with HbA1. Although the absolute value of HbA1 in the present study may not be currently clinically relevant, this does not alter our findings regarding inter-relationships of the various biomarkers as well as associations to mortality. The glycemic measurements in the study were obtained cross-sectionally allowing association testing only. A potential source of bias stems from the fact that although the original samples were obtained in a systematic, stratified manner from the study population, the group studied may not be strictly representative. However, the distribution of participants undergoing OGTT was not statistically different from that of the original sample with respect to age, sex and ethnic origin. Finally, participants underwent an OGTT after an overnight fast with a 100 g glucose, instead of the standard 75 g. Nevertheless, because the additional glucose load had little effect on the glucose level [9] but enhanced the insulin response [10], it was not expected to influence the use of the clinical threshold of 200 mg/dL for diabetes.

Identifying those at an early point in their evolution to worsening dysglycemia may therefore have the greatest benefit of preserving β-cell function and hence preventing or reversing an otherwise ineluctable decline towards diabetes and increased mortality. Although further prospective studies will be required to confirm the present observations, in the interim, it may be prudent to include a 1 h glucose level during an OGTT to avoid underestimating the severity of glycemic disorders that may occur with sole usage of the 2 h post-load value. Although the optimal method for screening and diagnosing glucose disorders has not been established, the combination of HbA_{1c} plus fasting plasma glucose has been reported to improve identification of those at risk for progression to diabetes [29]. Inclusion of the 1 h level may further refine our ability to identify high-risk individuals.

Acknowledgements

We are grateful to Michelle Bravo and Navneet Sahota for their expert help in formulating and editing Figure 1.

Author contributions

MB and RD wrote the manuscript. AC and RD researched the data. JR provided a critical review of the analysis. RD and AC are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

Appendix

Mean plasma values according to HbA1 quintiles of 1226 non-diabetic individuals [HbA1 range %]

	N	Total [3.4–11.0]	Q1 [3.4–6.0]	Q2 [6.1–6.5]	Q3 [6.6–7.1]	Q4 [7.2–7.7]	Q5 [7.8–11.0]	*p* (correlation)
FPG, mg/dL	1226	97.9	95.6	96.2	98.1	99.1	100.3	<0.0001
GT 1 hour, mg/dL	992	142.1	134.5	133.7	142.8	149.0	150.4	<0.0001
GT 2 hour, mg/dL	994	114.4	112.2	109.6	114.3	116.4	119.4	<0.0001
Fast insulin, mU/L	1158	14.5	14.3	13.9	13.6	15.0	15.9	0.01
1 h insulin, mU/L	926	80.5	79.9	73.2	82.9	78.1	88.2	0.15
2 h insulin, mU/L	918	72.3	71.1	65.3	73.0	72.6	79.4	0.04
BMI, kg/m^2	1220	25.9	25.6	25.8	26.0	25.8	26.2	0.04
Systolic BP, mmHg	1209	132.7	133.8	131.9	130.8	133.1	133.9	0.64
Diastolic BP, mmHg	1209	85.4	86.1	84.8	84.5	86.4	85.1	0.92
Total cholesterol, mg/dL	1198	216.3	218.6	209.2	220.9	215.6	217.3	0.66
HDL cholesterol, mg/dL	902	43.8	42.4	42.1	43.4	44.7	45.7	0.002
Male	469	40.7	38.8	40.6	38.5	42.1	42.8	0.005
Female	433	47.0	45.9	44.2	47.7	48.2	48.5	0.08
Triglycerides, mg/dL	1197	129.9	127.9	125.9	128.3	133.2	134.0	0.47
HOMA-IR*	1158	3.5	3.4	3.3	3.3	3.7	4.0	0.001
HOMA1-B%**	1158	50.2	50.2	49.0	46.7	51.5	53.4	0.15
Metabolic syndrome (%) ***	1226	13.6	13.7	12.1	11.3	13.5	17.2	0.3∼
Mortality (%)	1226	51.3	49.0	48.1	48.2	51.9	58.8	0.08∼

*HOMA1-IR = (FPI × FPG × 0.05551) / 22.5.
**HOMA1-B% = (20 × FPI) / (FPG × 0.05551 − 3.5), where FPI is fasting plasma insulin (mU/L) and FPG is fasting plasma glucose (mg/dL).
***Defined by ATP III criteria (ref. 12); ∼*p* derived from the one-way ANOVA test.
To convert mg/dL to mmol/L divide by 18 or multiply by 0.05551.

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