Recent population changes in HbA_{1c} and fasting insulin concentrations among US adults with preserved glucose homeostasis

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Received: 12 February 2010 / Accepted: 23 April 2010 / Published online: 27 May 2010
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Abstract

Aims/hypothesis Although diagnosed type 2 diabetes has increased in the past decade, little is known about accompanying changes in fasting plasma glucose (FPG), HbA_{1c} and fasting serum insulin (FI) levels in the non-diabetic population.

Methods Using population estimates from National Health and Nutrition Examination Surveys, we compared distribution of FPG, HbA_{1c} and FI in non-diabetic US persons who were ≥20 years old in 1999 to 2006 with that in persons of the same age in 1988 to 1994.

Results Age-, sex- and race-adjusted mean FPG levels between the two study periods did not change, but mean HbA_{1c} and FI levels increased (0.10% and 4.8 pmol/l, respectively; $p < 0.001$ for both). The increased HbA_{1c} level was driven largely by an upward shift in the lower end of the HbA_{1c} distribution. In contrast, the increased FI level was driven primarily by an upward shift in the middle and higher end of FI distribution, especially among persons aged 20 to 44 years. After adjustments for BMI or waist circumference, the increase in the mean HbA_{1c} level was attenuated (0.06%; $p < 0.001$), whereas the mean FPG level decreased by 0.1 mmol/l ($p < 0.001$) and the mean FI level no longer demonstrated significant change.

Conclusions/interpretation Despite little change in the distribution of FPG levels, HbA_{1c} and FI levels increased in the non-diabetic population in the past decade. The increase in FI levels suggests that levels of insulin resistance were greater among US adults, especially young adults, than in the previous decade.

Keywords Distribution · Glucose · Haemoglobin HbA_{1c} · Insulin · Type 2 diabetes

Abbreviations

FI	Fasting serum insulin
FPG	Fasting plasma glucose
NHANES	US National Health and Nutrition Examination Survey

Introduction

While concentrations of fasting insulin have increased among non-diabetic US adults [1], a corresponding increase in the prevalence of prediabetes has not been found [2]. The lack of increase in the prevalence of prediabetes may be because normal levels of fasting plasma glucose (FPG) are preserved in persons without diabetes by homeostatic mechanisms (e.g. an increase in insulin levels) until shortly before they develop diabetes. Understanding secular changes in light of glucose homeostatic mechanisms among persons without diabetes may help researchers identify indicators for tracking the effectiveness of public health strategies to prevent type 2 diabetes.

We examined changes in FPG, HbA_{1c} and fasting serum insulin (FI) levels in the US non-diabetic population between two time periods: 1988 to 1994 and 1999 to

Electronic supplementary material The online version of this article (doi:10.1007/s00125-010-1800-2) contains supplementary material, which is available to authorised users.

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2006. Our objective was to determine at the population level whether changes in these measures follow patterns similar to those for glucose homeostasis as currently conceived for individuals [3].

Methods

Data source We compared the US National Health and Nutrition Examination Survey (NHANES) data for 1988 to 1994 with NHANES data for 1999 to 2006. NHANES is a series of cross-sectional, nationally representative surveys among non-institutionalised civilian residents. Half of the participants are randomly assigned to a morning examination at which their blood is drawn after fasting. A total of 35,559 persons participated in NHANES during the two study periods (16,573 from 1988 to 1994, 18,986 from 1999 to 2006). After pregnant women had been excluded (288 from the 1988–1994 sample, 1,097 from the 1999–2006 sample), 15,257 (7,703 from the earlier period, 7,554 from the later period) provided morning fasting blood samples, from which valid FPG, HbA_{1c} and FI measurements were obtained for 14,421 participants (7,005 and 7,416 from the earlier and later samples respectively). Of these, we excluded participants who reported having physician-diagnosed diabetes (1,199) and those with FPG $\geq$ 7.0 mmol/l (536). Our final sample of US adults without diabetes thus consisted of 12,686 NHANES participants (6,186 for 1988–1994, 6,500 for 1999–2006).

Measures of glucose homeostasis indicators The survey participants had their FPG, FI and HbA_{1c} concentrations measured after fasting for at least 8 h but not longer than 24 h. FPG was assayed enzymatically from plasma by the hexokinase method. In both time periods HbA_{1c} measurement was standardised to the reference method used for the DCCT [4]. From 1988 to 1994 and 1999 to 2002, FI was assayed from serum by radioimmunoassay with the double-antibody batch method; the two-site immunoenzymometric method was used in 2003 to 2006. To minimise systematic measurement differences associated with variations in assay methods or kits, we applied the adjustment procedure and equations provided by NHANES to these measurements to make them comparable across surveys [4].

Other variables Body mass index (kg/m²) was calculated from measured body weight and height, and waist circumference was measured just above the uppermost lateral border of the ilium. Race/ethnicity was classified into four groups (non-Hispanic white, non-Hispanic black, Mexican American or other).

Statistical analysis We used a software package (SAS-Callable SUDAAN, version 9.0.1; Research Triangle Institute, Research Triangle Park, NC, USA) to account for complex sampling design and to obtain point estimates and standard errors applicable to the US population.

To obtain plots of the per cent of the population and cumulative per cent of the population, we used the 2.5 and

Table 1 Geometric means of and absolute changes in FPG, HbA_{1c} and FI among non-diabetic US adults: NHANES 1988–1994 and 1996–2006

Measurements	NHANES 1988–1994		NHANES 1999–2006		Absolute change	<i>p</i> value
	<i>n</i>	Mean (95% CI)	<i>n</i>	Mean (95% CI)		
Crude						
FPG (mmol/l)	6,186	5.26 (5.20–5.28)	6,500	5.27 (5.25–5.30)	0.01	0.441
HbA _{1c} (%)	6,167	5.19 (5.16–5.22)	6,489	5.29 (5.28–5.31)	0.10	<0.001
FI (pmol/l)	6,186	52.08 (50.04–54.12)	6,500	57.36 (55.98–58.80)	5.28	<0.001
Adjusted for ^a						
FPG (mmol/l)	6,186	5.27 (5.26–5.29)	6,500	5.27 (5.24–5.29)	0.00	0.689
HbA _{1c} (%)	6,167	5.20 (5.17–5.22)	6,489	5.29 (5.27–5.30)	0.09	<0.001
FI (pmol/l)	6,186	52.32 (50.34–54.30)	6,500	57.12 (55.74–58.62)	4.80	<0.001
Adjusted for ^b						
FPG (mmol/l)	6,175	5.29 (5.27–5.31)	6,383	5.25 (5.22–5.27)	−0.06	0.005
HbA _{1c} (%)	6,156	5.21 (5.18–5.23)	6,372	5.27 (5.26–5.29)	0.06	<0.001
FI (pmol/l)	6,175	54.84 (52.86–56.82)	6,383	54.90 (53.64–56.22)	0.06	0.917
Adjusted for ^c						
FPG (mmol/l)	5,983	5.29 (5.27–5.31)	6,326	5.25 (5.22–5.27)	−0.06	0.002
HbA _{1c} (%)	5,965	5.21 (5.18–5.24)	6,315	5.27 (5.25–5.29)	0.06	<0.001
FI (pmol/l)	5,983	55.20 (53.22–57.24)	6,326	54.42 (53.16–55.74)	−0.78	0.470

^a Age, sex and race/ethnicity; ^b age, sex, race/ethnicity and BMI; ^c age, sex, race/ethnicity and waist circumference

97.5 percentiles of the distributions as cut-off points to define the lowest and highest groups, and divided the population between these percentiles into ten groups with equal increments.

Polytomous logistic regression was used to estimate the adjusted probability of a person being classified into each group and to obtain predicted percentages of study population. We used Tukey mean difference plots to show the distribution shifts by age groups (Electronic supplementary material [ESM] Methods).

Results

Between the two study periods, the estimated mean BMI of US adults without diabetes increased by 1.7 kg/m² ($p < 0.001$), the estimated proportion of obese persons (BMI ≥ 30 kg/m²) increased from 20.7% to 29.6% ($p < 0.001$) and the estimated average waist circumference increased by 4.1 cm among men and 4.9 cm among women ($p < 0.001$ for both; ESM Table 1).

The adjusted geometric means of FPG were not significantly different between the two time periods ($p > 0.10$; Table 1). In contrast, adjusted mean HbA_{1c} and FI levels were significantly higher in the 1999 to 2006 period ($p < 0.001$). After further adjustment for BMI or waist circumference, the difference in the mean HbA_{1c} level remained significant, but not the difference in the mean FI levels.

Between two time periods, we found no change in the adjusted FPG distribution ($p > 0.8$ from the logistic regression; Fig. 1a). The lower end of HbA_{1c} distribution, and the middle and higher end of FI distribution shifted toward higher levels ($p < 0.001$ for both; Fig. 1b, c).

Upon adjustment for BMI or waist circumference, the HbA_{1c} distribution continued to show small upward changes ($p < 0.001$), while the shift in FI distribution was eliminated ($p > 0.10$).

The Tukey mean difference plot of FI (ESM Fig. 1) showed that FI distributions in all age groups shifted to the right from the earlier to the later survey, with the largest shift occurring among persons aged 20 to 44 years ($p < 0.001$).

Discussion

Our analyses of data from nationally representative samples of US adults indicate that the increased prevalence of type 2 diabetes has been accompanied by differing patterns of changes in FPG, HbA_{1c} and FI levels in the subpopulation without diabetes. Among non-diabetic adults we found no significant increase in the mean FPG level, but a greater mean HbA_{1c} level (driven by higher concentrations at the

Fig. 1 Age-, sex-, race/ethnicity-adjusted percentage (bar: 1988–1994 [grey columns] and 1999–2006 [white columns]) and cumulative percentage (line: 1988–1994 [solid line] and 1999–2006 [dashed line]) of non-diabetic US adults in each of 12 ranges of fasting plasma glucose (a), HbA_{1c} (b), and fasting insulin (c) levels, by NHANES survey period

lower end of the distribution) and a greater mean FI level (with higher concentrations at the upper end of the distribution).

Preservation of circulating FPG in a restricted range is important for survival and FPG is thus maintained within a tight range through changes in appetite, a variety of

hormonal and metabolic mechanisms, and changes in hepatic glucose output until some threshold of beta cell failure causes a glucose decompensation [5]. Persons who eventually develop type 2 diabetes do not typically have increased FPG until within 2 years prior to diagnosis [6]. However, their 2 h post-challenge glucose level increases approximately 5 years prior to diagnosis [6, 7]. Thus, in the earlier years prior to diagnosis, the underlying pathophysiological processes that eventually lead to type 2 diabetes are hidden by homeostatic mechanisms that tend to preserve normal levels of fasting or post-challenge glycaemia. Between 1988 and 1994, and 1999 and 2006, mean FPG levels changed very little, perhaps reflecting the robust compensatory mechanisms at work in the majority of people without diabetes. These mechanisms may also explain why the prevalence of type 2 diabetes is increasing in the US population, while the prevalence of prediabetes has been stable [2].

Interestingly, unlike the relatively stable distribution of FPG concentrations, the lower end of the distribution of HbA_{1c} concentrations increased between the two time periods, whereas the higher end of the distribution showed little change. Although it could not be examined with our data, we speculate that the recent reduction in the proportion of adults with very low HbA_{1c} values may be due to persons spending a smaller proportion of their time in the fasting state than in the previous decade.

These findings suggest that FI level may be more sensitive to lifestyle or environmental changes than HbA_{1c} or FPG levels and thus possibly an earlier indicator of diabetogenic trends in the population [6]. Our finding that the estimated increase in FI level disappeared after adjustment for BMI or waist circumference suggests that this increase was associated with the increasing adiposity of the US population. Further research could help confirm the feasibility of using obesity indices for this purpose.

Although NHANES data, collected via national cross-sectional surveys, are useful for analysing national trends, longitudinal follow-up studies are needed to identify early biomarkers of future type 2 diabetes that could be used to target prevention efforts before the appearance of hyperglycaemia. Our analysis included only the glucose homeostasis indicators available within the NHANES laboratory data, but alternative indicators might serve as well or better. Nevertheless, our findings are consistent with: (1) the pathophysiological mechanism believed to precede diabetes; (2) the homeostatic mechanisms at work in non-diabetic persons; and (3) the natural history of type 2

diabetes [3, 8, 9]. We did not include persons with diagnosed diabetes in our study because we wanted to minimise the effect of diabetes treatments on glucose levels of the study cohort. Furthermore, the relationship between glucose and insulin levels before the onset of diabetes is different from that after diabetes onset [10], so inclusion of persons with diabetes would have compromised our results.

In this study, despite little change in the distribution of FPG levels, HbA_{1c} and FI levels increased between the two survey periods. The increase in FI levels suggests greater levels of insulin resistance among US adults than in the previous decade, especially among young adults. The potentially diabetogenic circumstances of our times may be reflected earlier by FI measures than by changes in glucose levels.

Acknowledgements The authors thank the women and men who participated in the study. We would also like to thank all of the staff involved in the US National Health and Nutrition Examination Survey for the study design, data collection and data dissemination.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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