Int J Diabetes & Metabolism (2007) 15: 76-80

Gender: does it have role has a role in glycaemic control in Caucasians with well-controlled type 2 diabetes?

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Abstract
Background: Type 2 diabetes is costly to manage and thus it is important to know if management of blood glucose and HbA_{1c} are meeting clinical targets in both men and women. There is conflicting published data on the gender equality of blood glucose and HbA_{1c} management in type 2 diabetics. Objective: The purpose of this work was to review the literature on gender equality in blood glucose management and to test the hypothesis that management of blood glucose and HbA_{1c} would meet clinical targets in Cape Breton, Nova Scotia, irrespective of gender in well controlled Caucasian type 2 diabetic patients. Design, Setting and Participants: Fasting serum insulin and insulin sensitivity levels were determined in order to assist in the explanation of the glucose and HbA_{1c} results in people with diabetes. Patients were asked to give a fasting blood sample on each of two occasions three months apart. Results: There were no differences between males and females in each of fasting serum glucose (FSG) and HbA_{1c} levels as well as fasting serum insulin concentrations and in insulin sensitivity at visit 1 or 2. However, each of FSG and HbA_{1c} levels were slightly higher than clinical targets. Modestly elevated serum insulin and lower insulin sensitivity were consistent with the FSG and HbA_{1c} levels. This contrasts with some of the existing literature pointing out the need for a much larger study to be done in Cape Breton. Conclusion: It is concluded that blood glucose management among people with well controlled type 2 diabetes in Cape Breton, Nova Scotia may be close to clinical targets irrespective of gender. A further lowering of HbA_{1c} and FSG may be in order. However, this was only a very small study and a much larger one would answer whether there is gender equality in FSG and HbA_{1c} among persons with well controlled type 2 diabetes on Cape Breton Island.

Introduction

Cape Breton Island in the province of Nova Scotia, Canada suffers from among the highest rates of type 2 diabetes in Canada, the consequences of which are seen in the overall economy and in the competition for health care dollars with other health issues. Consequently it is important to control this disease as much as possible so as reduce its economic and social impact. There are no reports to date as regarding equity of management of glycaemia in type 2 diabetes by gender on Cape Breton Island, such information being of clear importance for the medical, economic and social impacts of this disease.

Type 2 diabetes is partially characterised by elevated fasting blood serum glucose (FSG) and insulin concentrations (in most cases), the percentage of haemoglobin as $A1_C$ (HbA_{1c}) and decreased insulin sensitivity.[1,2,3,4] Insulin insensitivity is frequently brought on by obesity or being overweight which results in a reduction in insulin receptor and post-insulin binding signalling transduction mechanisms.[5,6,7,8] The response of the pancreas to insulin insensitivity is to increase the blood serum concentration of insulin.[9, 10,11] However this rise in insulin levels seldom compensates completely for the insulin insensitivity and consequently blood serum glucose concentrations rise.[12,13,14,15] When blood serum glucose concentrations rise there is an increase in glycosylated HbA_{1c} as there is an increased ratio to glucose to haemoglobin concentration thus allowing the glycosylation process to occur at a higher rate.[16,17,18,19]

The small body of existing literature on glycaemic control by gender presents conflicting views on whether there is equality among the sexes. Pouwer and Snoek,[20] Pomerleau et al,[21] Abdelmoneim and Al-Homrany,[22] Nielsen et al, [23] all report gender inequity in glycaemic control while Kobayashi et al.[24] and Jonsson et al.[25] Banerji et al [26] showed no difference. Interestingly, assessment of glucose management by gender is also of interest to at least one other research group[27] suggesting that this is a topic worthy of exploration. Thus, the results of glycaemic control by gender vary from study to study making this study critical. It is hypothesised that there is no difference in gender regarding glycaemic control in Caucasian type 2 diabetics on Cape Breton Island.

Type 2 diabetes is costly to manage and thus it is important to know if management of blood glucose and HbA_{1c} meet clinical targets in both males and females. Presently there appear to be no studies addressing whether there are any gender differences in FSG, HbA_{1c}, insulin or insulin sensitivity levels. The purpose of this work was to test the

Received on: 2/5/2007
Accepted on: 10/11/2007

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hypothesis that each of male and female patients with type 2 diabetes were meeting clinical targets in terms of each of fasting blood serum glucose and HbA_{1c}. Hence it was also important to know if there are any gender-mediated differences in any of these parameters so as to decide which parameters might deserve more aggressive treatment in one sex over the other. Fasting blood serum insulin and insulin sensitivity levels were determined to assist in the explanation of the FSG and HbA_{1c} results.

Methods

Subjects (n =20 male, 20 female) type 2 patients with diabetes who were not on insulin therapy were randomly chosen from among 84 Caucasians responding in approximately equal sex numbers to a Sydney, Nova Scotia newspaper advertisement and two area physicians. Of these patients 18 males and 14 females completed the two required visits to determine stability in FSG, insulin, HbA_{1c} or insulin sensitivity. None of the females were of reproductive age. This study received approval from the Cape Breton University Human Ethics Review Committee. Subjects came fasted (12-14 hours) for visit 1 and 3 months later for visit 2. There was no change in any factor affecting the blood variables between visits one and two. On both visits, the age and sex of participants was noted and body weight and height as well as body mass index (BMI) were determined. Blood serum glucose concentrations were determined using Wako Chemicals (Richmond, VA, USA). Glucose C2 Auto enzymatic method kit and insulin by ELISA (Linco Research, St, Charles, MO, USA) following manufacturers' directions. HbA_{1c} was determined by HPLC.[28] Insulin sensitivity was calculated for an individual by dividing blood serum glucose concentration by the concentration of insulin at a given visit.

Statistical analyses

The data in tables 1-2 was analysed by a one-way analysis of variance for a given row of data in each of the tables.

Results

The patients' characteristics are found in Table 1. The values for each of visits 1 and 2 for all subjects combined and for males and females show no differences for the patients characteristics except for BMI (Table 1) and no differences in the whole group versus gender separation for each of glucose and HbA_{1c} levels as well as insulin sensitivity and insulin concentrations (Tables 2). It is important to note that the similarities in these values for each of visits 1 and 2 for the whole population (N= 32) are not masking any gender differences. Despite a higher BMI for females, the male and the female BMI values were gender consistent for visit 1 versus visit 2, a reflection of no change in factors affecting BMI. The higher BMI was not sufficiently so to manifest itself in male female differences for each of glucose and HbA_{1c} levels as well as insulin sensitivity and insulin concentrations (Tables 2). The glycaemic control data is consistent for a well-controlled population of people with diabetes for both males and females despite BMI levels that place these persons in the obese category. [11, 16,17]

Table 1: Age, Sex and BMI of subjects (all Caucasian). Data (n = 32) is reported as mean ± standard error of the mean for the patients who completed the trial. The superscripts indicate that female BMIs were higher than males for each of visits one and two.

	All subjects	All males	All females
Age (years)	59.5 ± 1.7	60.7 ± 2.9	58.3 ± 1.7
Sex (M/F) n=	32	18	14
Body mass index (BMI) kg/m^2 visit 1	32.4 ±0.9	30.3 ± 0.7	34.7 ± 1.6[a]
Body mass index (BMI) kg/m^2visit 2	32.2 ± 1.0	30.3 ± 0.8	34.4 ± 1.7[a]

Discussion

The data indicate that there is no difference between males and females in FSG or HbA_{1c} levels consistent with similar concentrations of serum insulin and decreased insulin sensitivity. The elevated levels of insulin and its inefficient use (decreased insulin sensitivity) explain the elevated levels of FSG. Elevated FSG results in increased rates of Schiff base reaction with haemoglobin followed by an Amadori rearrangement, which manifests itself in increased levels of HbA_{1c}. [29,30,31,32] HbA_{1c} is a sensitive indicator of blood glucose concentrations over the last three months. [33,34,35,36,37] FSG and HbA_{1c} are stable as are their determinants of insulin concentration and insulin sensitivity or the 3-month period for both males and females. Consequently, both genders are being managed equally well and stably so over time. Thus there seems to be reasonably good compliance on the part of patients toward appropriately prescribed dietary, exercise and medication measures directed at the control of FSG, and hence HbA_{1c}, through manipulation of insulin levels and insulin sensitivity.

Elevated BMI is associated with higher glucose and insulin concentrations and HbA_{1c} levels as well as lower insulin sensitivity (Table 2). However, despite the higher BMI levels found in females than males this did not manifest in worse glycaemic control. It may be that as one rises above a BMI classification of obesity of 30.0, relatively small (~ 2 kg/m^2 in this case) but statistically differences in BMI do not manifest in clinically significant worse glycaemic control. [38,39]

The literature is mixed on gender determined glycaemic control in type 2 diabetes. Some reports[20,21,22,23] show gender inequality while others[24,25,26] have indicated no difference between males and females. Among those indicating gender inequality, one study indicated that depressed women had worse glycaemic control than depressed men in one group studied but the opposite was true in another group examined.[20] Differences in glycaemic control in type 2 diabetes by gender and ethnic origin have been noted in a study comparing serum glucose responses to a glucose load test.[21]

Table 2: Comparison of fasting blood serum glucose and insulin concentrations, insulin sensitivity and HbA1c levels in all type 2 diabetics and male versus female type 2 diabetic patients in Cape Breton, Nova Scotia coming for two visits 3 months apart. Data (n = 32) is reported as mean ± standard error of the mean.

Parameter	All subjects visit 1	All subjects visit 2	All males visit 1	All males visit 2	All females visit 1	All females visit 2
Number	32	32	18	18	14	14
Glucose (mmol/L)	8.4 ± 0.6	8.0 ± 0.6	8.3 ± 0.9	8.1 ± 1.1	8.6 ± 0.8	8.3 ± 0.6
Insulin concentrations (μU/mL)	10.0. ± 1.2	10.4 ± 1.7	9.0 ± 1.3	10.2 ± 1.9	10.9 ± 1.8	10.6 ± 2.2
Insulin sensitivity ([glucose]/[insulin])	0.8 ± 0.1	0.7 ± 0.1	0.9 ± 0.2	0.8 ± 0.2	0.8 ± 0.1	0.7 ± 0.1
HbA_{1c} (%)	7.2 ± 0.4	7.3 ± 0.4	6.8 ± 0.7	7.2 ± 0.4	7.5 ± 0.5	7.3 ± 0.6

Thus the tool used to measure glycaemic control is critical and must take into account gender differences in metabolic response as it relates to fasting serum glucose. This appears not to be the case in all races[26]. Gender differences in health education and higher female BMIs led to worse glycaemic control in females.[22] Furthermore, routine care for women resulted in a poorer glycaemic control compared to men.[23] However, in another study men and women had equal glycaemic control despite the fact that women had more frequent outpatient contacts with the healthcare system than men. Structured personal care was equally effective in men and women in terms of glycaemic control.[23] There appear to be no studies examining gender determined glycaemic control that take into account various socioeconomic factors (e.g. race, education, income, wealth) though such studies are clearly needed. None of the factors indicated in this paragraph could be taken into account in the small sample of Caucasians obtained from Cape Breton but clearly these factors should form the basis of a further larger study on this island. A much larger sample size would provide more extensive information.

The data gathered from Cape Breton indicated that Caucasian patients were close to meeting clinical target points for FSG and HbA_{1c}. However, even if people with type 2 diabetes meet clinical targets in terms of glycaemic control, there is still a benefit to be realised by further reductions toward glycaemic control levels found in non-diabetic individuals. Such benefits include a reduced risk of cardiovascular complications (e.g. hypertension, dyslipidaemia, myocardial infarction), stroke, neuropathy, microangiopathy, retinopathy, nephropathy and possibly near or total complete loss of endogenous insulin production similar to type 1 diabetes.[40,41,42,43]

In conclusion, blood glucose management among the thirty two Caucasians with type 2 diabetes sampled in Cape Breton, Nova Scotia appears to be very close to clinical targets and is equally so in males and females. However, further lowering of FSG and HbA_{1c} levels would further benefit both male and female type 2 diabetic patients in terms of reducing glycaemic control complications,. Whether such benefits would arise from better patient compliance with diet, exercise and medications or from better tools available to physicians remains to be determined. Furthermore, it is important to note that this was a relatively small sample of the total type 2 diabetic population and one which may in any event be highly motivated, as evidenced by their willingness to participate in the study. Nonetheless, if these data are truly representative of the overall type 2 diabetic population on Cape Breton Island, it appears that the combination of skilled physicians and motivated type 2 diabetic patients are making serious efforts to reduce the impact of this disease. However, it may still be possible to realise even better glycaemic control and hence further reduce the medical, social and economic consequences of this disease. Additionally, a larger study should be undertaken on Cape Breton and elsewhere to assess glycaemic control by gender, further stratified by race, education, wealth and income.

Acknowledgments

Ms. Pat Collins, R.N. of the Cape Breton University Health Centre is thanked for helping with blood taking and anthropometric measures. The authors also acknowledge the contribution of Dr. J. Wawrzyszyn of Sydney for drawing this study to the attention of his patients. We also thank Dr. E. Rudiuk of Cape Breton University for his assistance with statistical analyses. Financial support of this study was from the Cape Breton University RAP grant. The Canadian Institutes of Health Research generously contributed to the Cape Breton University RAP grant funds to make this study possible.

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