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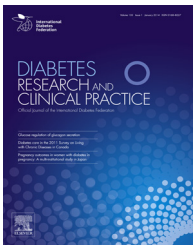

Country of birth modifies the association of fatty liver index with insulin action in Middle Eastern immigrants to Sweden

Louise Bennet [a,b,c,*], *Leif Groop* [a,d], *Paul W. Franks* [a,c,e,f]

[a] *Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden*
[b] *Family Medicine, Lund University, Malmö, Sweden*
[c] *Genetic and Molecular Epidemiology Unit, Lund University Diabetes Centre, Malmö, Sweden*
[d] *Department of Diabetes and Endocrinology, Lund University Diabetes Centre, Malmö, Sweden*
[e] *Department of Nutrition, Harvard School of Public Health, Boston, MA, USA*
[f] *Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden*

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ABSTRACT

Aims: Non-alcohol fatty liver disease (NAFLD) is a strong risk factor for insulin resistance and type 2 diabetes. The prevalence of NAFLD varies across populations of different ethnic backgrounds but the prevalence in Middle Eastern populations, which are at high risk of type 2 diabetes, is largely unknown. Using fatty liver index (FLI) as a proxy for NAFLD the aim was to calculate the odds of NAFLD (FLI $\geq$ 70) given country of origin and further to investigate the associations between ISI and FLI.

Methods: In 2010–2012 we conducted a population-based study of individuals aged 30–75 years born in Iraq or Sweden, in whom anthropometrics, fasting blood samples and oral glucose tolerance tests were performed and sociodemography and lifestyle behaviors characterized.

Results: A higher proportion of Iraqis (N = 1085) than Swedes (N = 605) had a high probability of NAFLD (FLI $\geq$ 70, 32.5 vs. 22.6%, $p < 0.001$, age- and sex-adjusted data) and ISI was more severely impaired (70.7 vs. 95.9%, $p < 0.001$). Independently of traditional risk factors for NAFLD, being born in Iraqi increased the risk of FLI $\geq$ 70 (OR 1.59: 95% CI 1.15, 2.20). Furthermore, country of birth presented a stronger association between ISI and FLI $\geq$ 70 in Iraqis than in Swedes ($P_{interaction}$ = 0.019).

Conclusions: Our data indicate that immigrants from Iraq are at higher risk of NAFLD. The finding that country of birth modifies the relationship of FLI with ISI, suggests that liver fat may be a stronger determinant of impaired insulin action and increased risk of type 2 diabetes in Iraqis than in Swedes.

* Corresponding author at: Center for Primary Health Care Research, Clinical Research Centre, Building 28, Floor 11, Jan Waldenströms gata 35, Skåne University Hospital, 205 02 Malmö, Sweden. Tel.: +46 40 391367; fax: +46 40 391370.
E-mail address: Louise.Bennet@med.lu.se (L. Bennet).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CIR, corrected insulin response; DIo, disposition index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; IQR, interquartile range; ISI, insulin sensitivity index; LDL, low-density lipoprotein; p, plasma; SD, standard deviation; TGs, triglycerides.

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1. Introduction

Immigrants from the Middle East represent the largest non-European immigrant group to Sweden and are, compared to the native Swedish population, at high risk of impaired insulin action and type 2 diabetes [1]. The higher prevalence is partly explained by an excess prevalence of abdominal obesity and family history of diabetes; nonetheless, our data has shown that being born in Iraqi is an independent risk factor for diabetes [2]. Furthermore, the MEDIM (impact of Migration and Ethnicity on Diabetes in Malmö) study has shown that insulin sensitivity index (ISI) is lower in Iraqis than in Swedes, and that ISI may have a stronger impact on type 2 diabetes risk in Iraqis than in Swedes [1]. The lower ISI values in immigrants from Iraq are not fully explained by traditional risk factors such as family history of diabetes, abdominal obesity or physical inactivity, as illustrated by the fact that in individuals with a normal waist circumference and/or body mass index (BMI), ISI is more impaired than in Iraqis than in Swedes with equivalent levels of adiposity [1]. This suggests that mechanisms other than abdominal obesity or other traditional risk factors for insulin resistance may influence insulin action in Iraqis.

The mechanisms underlying the profound insulin resistance in the Iraqi born population are poorly understood, which motivated the current study. Whilst insulin action is influenced by abdominal and visceral obesity, other organs such as peripheral muscle and the liver are also involved [3]. For instance, non-alcohol fatty liver disease (NAFLD) represents a strong risk factor for impaired insulin action, pre-diabetes and type 2 diabetes [4]. Patients diagnosed with NAFLD also have a higher release of inflammatory markers than patients without NAFLD [5] and they also have a higher risk of cardiovascular disease (CVD) [6]. These results are in consistency with previous findings from the MEDIM study, showing that the association between lower ISI and inflammatory markers – such as cytokines – irrespective of other risk factors [7] is stronger and that the prevalence of CVD in diabetics is higher in Iraqis than in Swedes [8]. Altogether these findings indicate that NAFLD may be more prevalent and have a greater impact on insulin action and diabetes risk in Iraqis than native Swedes.

Globally, NAFLD is the most prevalent type of liver disease [9–11] and its prevalence differs according to ethnic background [12], with 12 to 15% in Asians [13] and 30% in Americans [14] affected. Although the characteristics of the Iraqi immigrant population resemble those of patients with NAFLD, the prevalence of NAFLD and association with insulin action in Middle Eastern populations has to the best of our knowledge not been investigated before. Thus, using the fatty liver index (FLI) as a proxy for NAFLD [15], in the MEDIM study we determined whether FLI levels differed between immigrants from Iraq and native Swedes and sought to characterize the factors underlying these differences. Further, we sought to study associations between insulin sensitivity index (ISI) and FLI.

2. Subjects

Citizens of Malmö born in Iraq and aged 30 to 75 years were randomly selected from the census register and invited by mail and phone to participate in a population-based survey. According to the census register, the population of Iraqi immigrants 30 to 75 years of age in Malmö consisted in 2010 of 4397 persons with a mean age of 44.8 years and of whom 57.8% were men. Swedish born citizens living in the same geographical area in Malmö were randomly selected from the census register to reach a similar age and gender distribution as the Iraqi population (mean age 45.2 years, $p = 0.08$; 57.4% males $p = 0.74$). Iraqi and Swedish individuals were then contacted and invited by mail and phone to participate in the study. We aimed to recruit a final sample of 2:1 Iraqi and Swedish participants with the goal to reach a similar age and sex distribution amongst the final participants as amongst the original background population. People with type 1 diabetes, severe physical or mental illness or disabilities were excluded from the study. A prerequisite for inclusion in the study was also that all values included in the FLI (gamma-glutamyl transferase (p-GGT), BMI, waist circumference and/or plasma triglycerides (p-TG)) were assessed.

To minimize cohort effects and assessment biases, examinations were conducted within a relatively short time-frame (February 1, 2010 through December 31, 2012). A flow chart describing the recruitment and participation rate of MEDIM is presented in a supplementary figure. All participants conducting an oral glucose tolerance test (OGTT) that did not have excessive alcohol habits (<9 standard glasses/week for women and <14 standard glasses/week for men) were included in the study.

3. Materials and methods

3.1. *Physical examination*

Standard physical examinations were performed by trained Swedish- and Arabic-speaking research nurses and clinical variables such as blood pressure, height, weight, waist circumferences, BMI and abdominal obesity were assessed and defined as previously described [16,17].

3.2. *Blood samples and oral glucose tolerance tests*

Participants were instructed to be fasting and not to eat or drink anything but water and not to use tobacco after 10 pm the day before testing. In the following morning, fasting blood samples were taken and a 75-g OGTT was performed and blood samples for plasma glucose and serum insulin at 30, 60, 90 and 120 min were collected thereafter. Blood glucose, serum insulin, HbA1c, total cholesterol, p-TG, high-density lipoprotein cholesterol (p-HDL) and low-density-lipoprotein cholesterol (p-LDL) levels were determined as previously described [16,18]. Plasma alanine aminotransferase (p-ALT, IU/L), aspartate aminotransferase (p-AST, IU/L) and gamma-glutamyl transferase (GGT, IU/L) were measured using a Cobas analyzer (Roche Diagnostics, Mannheim, Germany).

Normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), impaired glucose regulation (IGR, IFG in combination with IGT) and type 2 diabetes were defined according to World Health Organization criteria [19]; NGT, fasting glucose level of <6.1 mmol/L and a