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Glucose regulation and pain in older people—The Helsinki Birth Cohort Study

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ABSTRACT

Aims: To assess if individuals with diabetes or prediabetes report more pain or have increased use of pain medication compared to normoglycaemic individuals.
Methods: Using cross-sectional data, we studied 928 men and 1075 women from the Helsinki Birth Cohort Study in 2001–2004 at a mean age of 61.5 years. Glucose regulation was assessed with a 2-h 75 g oral glucose tolerance test, and applying World Health Organization criteria, participants were defined as having normoglycaemia, prediabetes (impaired fasting glucose or impaired glucose tolerance), newly diagnosed diabetes or previously diagnosed diabetes. Self-reported pain intensity and interference during the previous 4 weeks was estimated using the RAND 36-Item Health Survey 1.0. Information on use of pain medication during the past 12 months was obtained from the Social Insurance Institution of Finland.
Results: There was no difference in pain intensity or interference between glucose regulation groups for neither men nor women after adjusting for covariates (age, body mass index, education years, Beck Depression Inventory and physical activity). In addition, use of pain medication was similar between glucose regulation groups.
Conclusions: Although pain is a common symptom in the general population, impairments in glucose regulation alone does not seem to increase pain among older individuals.

1. Introduction

In the general population, pain is a common problem and an important reason for seeking medical attention [1]. The prevalence of chronic pain in European countries at population level has been estimated to be around 12–30% [2], but studies from individual countries have reported an even higher prevalence of more than 50% [3,4]. In Finland, chronic pain affects approximately 19–35% of the population [2,5] and pain is the primary symptom in nearly one third of the visits to health care centres [6]. Chronic pain has been shown to interfere with activities of daily living and is associated with poor self-rated health, as well as multimorbidity and premature mortality [7–9]. The economic consequences of pain are also substantial, both due to direct health care costs as well as indirect costs such as loss of work days and productivity [7,10]. As the prevalence of chronic pain has been shown to increase with older age, preventing and managing pain is important in order to decrease the risk of disability and loss of independence [3,11].

Chronic pain is common also among people with diabetes, as more than half report some type of chronic pain [12,13]. An important reason for this is peripheral neuropathy, which is a frequent complication of diabetes and has been reported to cause

Abbreviations: ATC, Anatomical Therapeutic Chemical; BDI, Beck Depression Inventory; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LTPA, leisure-time physical activity; NSAID, nonsteroidal anti-inflammatory drug; OGTT, oral glucose tolerance test; RAND-36, RAND 36-Item Health Survey 1.0.

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chronic pain in 13–26% of people with diabetes [14]. In addition to neuropathy, several non-neuropathic conditions and comorbidities associated with pain are often present in people with diabetes, including rheumatic diseases, osteoarthritis, fibromyalgia and depression [13,15–17]. In fact, we recently showed that comorbidities and depression, which frequently accompanies diabetes, might be more important causes of pain than diabetes itself [13].

Prediabetes, i.e. impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), progresses to diabetes with an annual rate of 5–10% and has been shown to be associated with morbidity and premature mortality [18]. The relationship between prediabetes and pain, however, is not well known. A previous study showed that regional as well as widespread chronic pain were not associated with prediabetes after adjusting for covariates, such as depression and obesity [19]. It has been hypothesised that hyperglycaemia present already in prediabetes may cause neuropathy and even painful neuropathy before the clinical onset of diabetes, but these findings have been inconsistent [14,20].

To further elaborate on this matter, we used objective measures of glucose regulation and assessed whether different stages of impairment in glucose regulation were associated with an increased prevalence of pain or use of pain medications compared to normoglycaemic older people at a mean age of 61.5 years. We hypothesised that pain intensity and interference would increase with more severe disturbances in glucose regulation.

2. Material and methods

2.1. Study population

This cross-sectional study was part of the Helsinki Birth Cohort Study and included data from a sub-cohort of 8760 individuals born between 1934 and 1944 at the Helsinki University Central Hospital. All cohort members attended child welfare clinics and were living in Finland in 1971, when Finnish residents were assigned a unique identification number [21]. In the year 2000, a sample of 2902 individuals were selected using random-number tables and invited to a clinical examination. This study included the 2003 individuals that participated in the clinical examination and were examined once between 2001 and 2004. All participants signed a written informed consent. This study complies with the guidelines of the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa, as well the National Public Health Institute.

2.2. Glucose regulation

At the clinical examination, fasting plasma glucose was measured in all participants. Those with a self-reported history of diabetes, a diabetes diagnosis in medical records, and those using medications for diabetes were defined as having previously known diabetes. All subjects underwent a standard 2-h 75 g oral glucose tolerance test (OGTT), except those with previously known diabetes. The World Health Organization criteria from 1999 were used to diagnose disturbances in glucose regulation [22]. IFG was defined as a fasting plasma glucose level of 6.1–6.9 mmol/l, IGT as a 2-h glucose level of 7.8–11.0 mmol/l, and diabetes as a fasting plasma glucose level of at least 7.0 mmol/l or a 2-h glucose level of over 11.0 mmol/l. Those with no prior diagnosis of diabetes meeting the criteria for diabetes at the clinical examination were defined as having newly diagnosed diabetes. Prediabetes was defined as having either IFG or IGT or both.

2.3. Pain and pain medication

Self-reported pain was assessed at the clinical examination using the pain scale from the RAND 36-Item Health Survey 1.0 (RAND-36) [23]. The two questions included were “How much bodily pain have you had during the past 4 weeks?”, assessing pain intensity and was scored on a six-level scale from “None” to “Very severe”, and “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?”, assessing pain interference and was scored on a five-level scale from “Not at all” to “Extremely”. The original response for each question was then recoded proportionally to a discrete scale ranging from 0 to 100, according to scoring instructions for RAND-36 [23]. A higher score indicated less pain intensity and interference.

Information on purchases of pain medication was obtained from the Social Insurance Institution of Finland. Anatomical Therapeutic Chemical (ATC) codes were used to search the register for pain medications. Records of prescribed drugs over the previous 12 month-period prior to the clinical examination were included. Pain medications were coded into three groups: 1. Nonsteroidal anti-inflammatory drugs (NSAID) and paracetamol; 2. Opioids, including weak, intermediate and strong opioids; 3. Neuropathic drugs, including gabapentinoids and tricyclic antidepressants.

2.4. Covariates and study variables

All participants were measured for height and weight, and body mass index (BMI) was calculated as kg/m^2. Current health status was evaluated by self-reported diagnosis of chronic diseases, including hypertension, cardiovascular disease, cancer, rheumatic disease, and depression. Questionnaires were used to collect information on occupational status, educational attainment, and lifestyle characteristics. The Beck Depression Inventory (BDI) was used to assess depressive symptoms at the time of examination. Physical activity was estimated using the validated Kuopio Ischaemic Heart Diseases Risk Factor Study 12-month leisure-time physical activity (LTPA) questionnaire [24]. The results are presented as number of days per week performing any LTPA, including both non-conditioning (e.g. walking, gardening, yard work) and conditioning (e.g. jogging, skiing, weightlifting). Self-rated health was assessed with the question “How would you rate your health during the past 4 weeks?” and was scored on a visual analog scale ranging from 0 to 100. A higher score indicated better self-rated health.

2.5. Statistical analysis

Data are presented as means with standard deviation (SD) and as counts with percentages. Statistical comparison between glucose regulation groups were done using Pearson’s chi-square or Fisher–Freeman–Halton test for categorical variables and analysis of variance for continuous variables. In the case of violation of the assumptions (e.g. non-normality) in continuous variables, a bootstrap-type test and confidence intervals were used. The normality of variables was evaluated using the Shapiro–Wilk W test. For the analysis of pain intensity and pain interference between glucose regulation groups, we adjusted for age, BMI, education years, BDI and LTPA. All analyses were performed using Stata version 15.1 (StataCorp., College Station, Texas, USA).

3. Results

The study population included 928 men and 1075 women (Table 1). The mean age for all participants was 61.5 (SD 2.9). A

Table 1
Characteristics of cohort members grouped by glucose regulation.

	Men (n = 928)					Women (n = 1075)				
	NG	Prediabetes	New DM	Known DM	p	NG	Prediabetes	New DM	Known DM	p
N	441	305	90	92		608	332	75	60	
Age (years), mean (SD)	61.3 (2.8)	61.9 (2.9)	61.5 (2.8)	61.1 (2.6)	0.013	61.3 (2.9)	61.8 (3.3)	62.3 (3.0)	61.2 (2.8)	0.007
Occupational status, n (%)					0.29					0.12
Working	245 (56)	157 (51)	51 (57)	38 (41)		340 (56)	161 (48)	35 (47)	24 (40)	
Unemployed	38 (9)	31 (10)	9 (10)	12 (13)		64 (11)	37 (11)	8 (11)	8 (13)	
Retired	158 (36)	117 (38)	30 (33)	42 (46)		204 (34)	134 (40)	32 (43)	27 (47)	
Education years, mean (SD)	12.6 (3.9)	12.5 (3.6)	12.0 (3.5)	11.8 (3.6)	0.16	12.2 (3.6)	12.0 (3.4)	11.2 (3.2)	11.5 (3.2)	0.072
BMI (kg/m^2), mean (SD)	26.4 (3.4)	27.7 (3.7)	29.7 (6.0)	30.7 (4.7)	<0.001	26.5 (4.6)	28.6 (4.8)	29.7 (5.5)	32.4 (6.0)	<0.001
Current smoker, n (%)	133 (30)	84 (28)	27 (30)	26 (28)	0.88	124 (20)	64 819)	16 (21)	17 (28)	0.46
Alcohol consumption, n (%)					0.090					0.048
None	37 (8)	19 (6)	6 (7)	9 (8)		42 (7)	19 (6)	10 (13)	7 (12)	
Less than once per week	118 (27)	74 (24)	28 (31)	38 (41)		318 (52)	171 (52)	44 (59)	37 (62)	
1–2 times per week	183 (42)	139 (46)	34 (38)	31 (34)		183 (30)	93 (28)	16 (21)	12 (20)	
3 times or more per week	101 (23)	73 (24)	21 (24)	14 (15)		63 (10)	47 (14)	5 (7)	4 (7)	
LTPA days/week, mean (SD)	2.8 (1.8)	2.6 (2.0)	2.5 (1.9)	2.3 (1.7)	0.072	2.6 (1.9)	2.3 (1.9)	2.4 (1.9)	2.8 (1.8)	0.046
Health status, n (%)										
Hypertension	103 (23)	97 (32)	46 (51)	64 (70)	<0.001	133 (22)	129 (39)	36 (48)	36 (60)	<0.001
Cardiovascular disease	32 (7)	31 (10)	12 (13)	26 (28)	<0.001	17 (3)	27 (8)	4 (5)	7 (12)	<0.001
Cancer	23 (5)	16 (5)	8 (9)	2 (2)	0.25	54 (9)	28 (8)	7 (9)	3 (5)	0.77
Rheumatic disease	11 (2)	7 (2)	2 (2)	0 (0)	0.57	18 (3)	5 (2)	5 (7)	1 (2)	0.082
Depression	45 (10)	28 (9)	5 (6)	13 (14)	0.26	81 (13)	45 (14)	12 (16)	16 (27)	0.041
Self-rated health (VAS), mean (SD)	78 (18)	76 (19)	77 (17)	73 (21)	0.15	75 (19)	74 (20)	76 (21)	71 (23)	0.26
BDI, mean (SD)	4.5 (4.4)	5.2 (4.6)	4.9 (4.5)	7.0 (6.0)	<0.001	6.2 (5.5)	6.9 (5.8)	6.8 (6.9)	7.9 (6.0)	0.063

NG = normoglycaemia; New DM = diabetes diagnosed at oral glucose tolerance test; Known DM = diabetes diagnosed before oral glucose tolerance test; BMI = body mass index; LTPA = leisure-time physical activity; VAS = visual analog scale; BDI = Beck Depression Inventory.

total of 92 (9.9%) men and 60 (5.6%) women had a previous history of diabetes. Based on the OGTT, prediabetes was diagnosed in 305 (32.9%) men and 332 (30.9%) women, whereas diabetes was diagnosed in 90 (9.7%) men and 75 (7.0%) women. For both men and women there were differences between the glucose regulation groups in relation to age, BMI and prevalence of cardiovascular disease and hypertension. In addition, prevalence of depression and alcohol consumption as well as LTPA differed between the glucose regulation groups, but only in women. Among men on the other hand, there was a significant difference in mean BDI score between the glucose regulation groups. There was no difference in self-rated health between the groups of glucose regulation for neither men nor women.

During the previous 4 weeks, pain of at least moderate intensity was reported by 15.0% of men and 21.6% of women. The mean intensity score was 78.2 (SD 24.1) among men and 73.4 (SD 24.9) among women, equivalent to an intensity of "very mild" to "mild". The mean score for pain intensity in each glucose regulation group is shown in Fig. 1. There was no difference in pain intensity across the glucose regulation groups (p = 0.56 for men and p = 0.96 for women) after adjusting for covariates.

Further, 10.0% of men and 14.1% of women reported that pain had interfered at least at a moderate level with their ability to work during the previous 4 weeks. Men and women reported a mean interference score of 87.7 (SD 21.1) and 84.0 (SD 21.7), respectively, corresponding to an interference of "not at all" to "a little bit". Fig. 2 illustrates the amount of pain interference in each glucose regulation group, with no significant difference between the groups (p = 0.16 for men and p = 0.57 for women) after adjusting for covariates.

Table 2 shows the use of pain medication across the glucose regulation groups. Among men, 22.2% had been prescribed pain medication during the previous 12 months, whereas the corresponding number was 30.8% among women. There was no significant difference in the use of pain medications between the different glucose regulation groups for neither men (p = 0.76), nor women (p = 0.64). The most commonly prescribed pain medications for both men and women were NSAID or paracetamol. Neuropathic pain medications were used by 1% of men and women in the newly diagnosed diabetes group and by none of those with previously known diabetes.

4. Discussion

In this cross-sectional study of older people, we found that moderate pain or pain with higher intensity occurred in one fifth of women and in nearly one sixth of men. However, pain did not markedly interfere with the participants' ability to perform their work. We found no increase in pain intensity or interference among people with prediabetes or diabetes compared to people with normoglycaemia. The use of pain medication was similar across the glucose regulation groups, with no increase in prescribed medications for neuropathic pain among those with diabetes or prediabetes. In addition, there was no difference in self-rated health between the different groups of glucose regulation. We found no indication supporting our hypothesis that more severe disturbances in glucose regulation would be associated with increased pain.

The prevalence of impaired glucose regulation in our study was similar to previous studies in the Finnish population. Saaristo et al. [25] reported that among men aged 55–64 years the prevalence of diabetes and prediabetes were approximately 17% and 27%, respectively. The corresponding numbers for women in the same age group were approximately 12% for diabetes and 20% for prediabetes. Compared to other European countries, the prevalence of diabetes and impaired glucose tolerance in Finland do not differ notably [26]. We found that approximately half of those with diabetes were previously undiagnosed, which in accordance with previous studies suggests that diabetes is underdiagnosed in Finland [25]. The prevalence of pain in our study was also similar to what has been reported in other European countries, with a mean prevalence of 19% for moderate to severe pain [2].

Contrary to our findings, diabetes has been associated with an increased prevalence of pain in previous studies. Mäntyselkä et al. [19] reported that diabetes was associated with a three-fold odds of chronic pain at multiple sites, but not with an increased odds of chronic regional pain. In a sample of 100 individuals with dia-

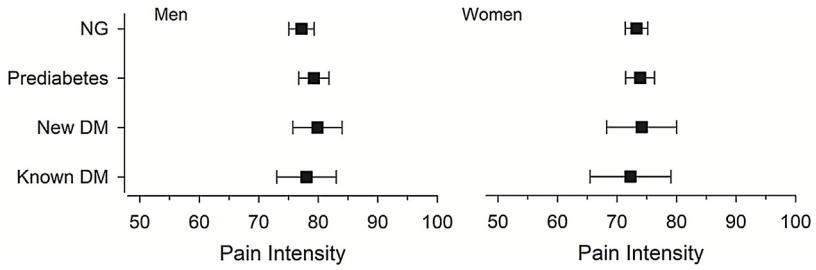

Fig. 1. Pain intensity for men and women across glucose regulation groups. Values were adjusted for age, body mass index, education years, Beck Depression Inventory and leisure-time physical activity. Whiskers indicate 95% confidence intervals. NG = normoglycaemia, New DM = diabetes diagnosed at oral glucose tolerance test, Known DM = diabetes diagnosed before oral glucose tolerance test.

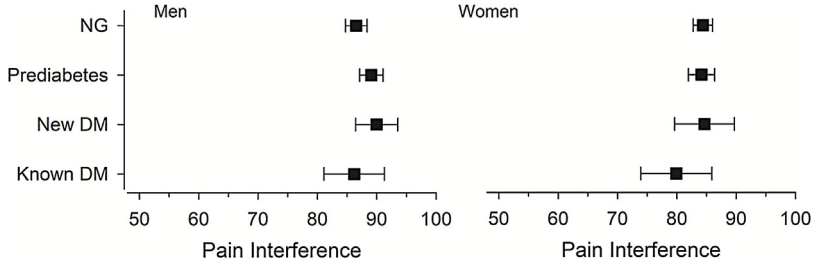

Fig. 2. Pain interference for men and women across glucose regulation groups. Values were adjusted for age, body mass index, education years, Beck Depression Inventory and leisure-time physical activity. Whiskers indicate 95% confidence intervals. NG = normoglycaemia, New DM = diabetes diagnosed at oral glucose tolerance test, Known DM = diabetes diagnosed before oral glucose tolerance test.

Table 2
Use of pain medication presented as frequencies and proportions.

	Men (n = 928)					Women (n = 1075)				
	NG (n = 441)	Prediabetes (n = 305)	New DM (n = 90)	Known DM (n = 92)	p	NG (n = 608)	Prediabetes (n = 332)	New DM (n = 75)	Known DM (n = 60)	p
Any pain medication	95 (22)	72 (24)	17 (19)	22 (24)	0.76	188 (31)	96 (29)	27 (36)	20 (33)	0.64
NSAID or paracetamol	90 (20)	68 (22)	17 (19)	18 (20)	0.86	184 (30)	91 (27)	26 (35)	18 (30)	0.61
Opioids	11 (2)	6 (2)	1 (1)	6 (7)	0.12	7 (1)	7 (2)	1 (1)	3 (5)	0.12
Neuropathic pain medication	4 (1)	2 (1)	1 (1)	0 (0)	0.88	7 (1)	3 (1)	1 (1)	0 (0)	0.89
Gabapentinoids	3 (1)	1 (1)	0 (0)	0 (0)		1 (0)	0 (0)	0 (0)	0 (0)	
Tricyclic antidepressants	2 (1)	1 (1)	1 (1)	0 (0)		6 (1)	3 (1)	1 (1)	0 (0)	

NG = normoglycaemia; New DM = diabetes diagnosed at oral glucose tolerance test; Known DM = diabetes diagnosed before oral glucose tolerance test; NSAID = nonsteroidal anti-inflammatory drug.

betes and 50 controls there was a significantly greater prevalence of fibromyalgia in those with diabetes, and fibromyalgia was also associated with a higher HbA_{1c} among those with diabetes [16]. Diabetes has also been associated with osteoarthritis and in a meta-analysis comprised of 49 studies, those with diabetes had a nearly 50% greater risk of having osteoarthritis compared to those without diabetes [27]. On the contrary, we have previously shown in a study including over 1000 individuals, that diabetes was not associated with pain after controlling for covariates [13]. Among those with diabetes, pain was more strongly associated with depressive symptoms and the number of comorbidities than with diabetes itself.

Although diabetic neuropathy has been found to be an important risk factor for chronic pain [28], we did not find an increase in the use of neuropathic pain medications among individuals with diabetes in our study. Duration of diabetes has been shown to increase the risk of neuropathy [14], but we found no difference in use of neuropathic pain medication or pain intensity between those with newly diagnosed diabetes and previously known diabetes. Thus, our findings suggest that neuropathy does not increase the burden of chronic pain for those with diabetes compared to those without diabetes. Some previous studies have also suggested that neuropathic pain may develop already at a stage of prediabetes, one reason for this hypothesis being that those with idiopathic neuropathy have an increased prevalence of prediabetes, in particularly IGT [29]. On the other hand, Dyck et al. assessed the association between objectively measured glucose regulation and neuropathy and found no increased prevalence of neuropathy for those with prediabetes compared to those with normoglycaemia [20]. Although we did not evaluate neuropathy in our study, we found no evidence suggesting increased amount of neuropathic pain among those with prediabetes compared to individuals with normoglycaemia, as both use of pain medication and pain intensity and interference were similar in both groups.

The absence of an association between impaired glucose regulation and pain in our study may be due to several reasons. First, we included any duration of pain that had occurred during the previous month, whereas many previous studies have included only chronic pain. This naturally excludes individuals with sub-chronic pain which could potentially occur often also among those with normoglycaemia and less severe impairments in glucose regulation. Second, studies relying solely on self-reported diagnosis of diabetes are unable to account for those with undiagnosed diabetes. These individuals may have less pain than those with a longer duration of diabetes, and this may cause bias in the association between diabetes and pain. Third, differences in sample age groups may cause varying results, as pain has been shown to increase with age [30,31].

Our results should encourage physicians to actively follow-up on glycaemic control and treatment of individuals with prediabetes and diabetes. Although diabetes is associated with several comorbidities, advances in the management of hyperglycaemia and other risk factors, as well as improved patient education may be a reason for improved overall health status for those with diabetes [32,33]. Effective primary prevention of neuropathy in diabetes and subsequently prevention of neuropathic pain could be one explanation why the use of neuropathic pain medication was low in our study population. The mean age of our sample was 61.5 years, and chronic pain may develop slowly over several years for individuals with impaired glucose regulation. Thus, by managing risk factors and comorbidities associated with diabetes and prediabetes it could be possible to slow down the development of chronic pain and minimise its intensity and progression [34,35].

This study has several strengths. We included over 2000 individuals, both men and women, from a well-characterised birth cohort. Glucose regulation was assessed objectively using OGTT, thereby diagnosing impairments in glucose regulation with high precision. Previous studies have shown that half of those with previously undiagnosed diabetes are diagnosed only by the OGTT and remain undiagnosed when assessing glucose regulation simply with fasting plasma glucose or HbA_{1c} [36]. Pain was assessed with the RAND-36, which is similar to the SF-36 Health Survey and one of the most widely used instruments to assess health related quality of life [37]. The survey is self-administered, easy to use and takes under 10 min to complete. It is a generic measure of health status and thereby not specific for age or disease. The surveys have also been validated and shown to be reliable in the Finnish general population [38].

The cross-sectional design of this study can be considered a weakness. We were unable to evaluate the long-term associations between impaired glucose regulation and the intensity and interference of pain. Therefore, we cannot exclude that impairments in glucose regulation increase the risk of pain as the individuals age. We acquired information on several different covariates, however, we were not able to assess the prevalence of complications associated with diabetes, including neuropathy. As ATC codes were used to access information on prescribed drugs, we were not able to exclude pain medications used for other indications than pain. We also acknowledge the possibility of a participation bias of healthier, community-dwelling participants in our study. The study population is a homogenous group of Caucasians of similar age from a restricted area in Finland, which should be taken into consideration when interpreting the results.

In conclusion, although pain is common among older people, disturbances in glucose regulation does not seem to increase the risk of pain compared to those with normoglycaemia. However, future longitudinal studies are needed to assess the long-term association between impaired glucose regulation and pain.

Author contributions

All authors participated in study conception and design. MBvB, MS and JGE planned and participated in data collection. MÅ and HK carried out statistical analysis. MÅ, MBvB, HK and JGE interpreted the data. MÅ wrote the first draft of the manuscript. All authors contributed to the critical review of the manuscript and have approved the final manuscript.

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Declarations of interest

None.

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