

Clinical Study

Elevated glycohemoglobin HbA1c is associated with low back pain in nonoverweight diabetics

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Abstract

BACKGROUND CONTEXT: Low back pain (LBP) is a common complaint in clinical practice of multifactorial origin. Although obesity has been thought to contribute to LBP primarily by altering the distribution of mechanical loads on the spine, the additional contribution of obesity-related conditions such as diabetes mellitus (DM) to LBP has not been thoroughly examined.

PURPOSE: To determine if there is a relationship between DM and LBP that is independent of body mass index (BMI) in a large cohort of adult survey participants.

STUDY DESIGN: Retrospective analysis of prospectively collected National Health and Nutrition Examination Survey (NHANES) data to characterize associations between LBP, DM, and BMI in adults subdivided into 6 subpopulations: normal weight (BMI 18.5–25), overweight (BMI 25–30), and obese (BMI >30) diabetics and nondiabetics. Diabetes was defined with glycohemoglobin A1c (HbA1c) $\geq 6.5\%$.

PATIENT SAMPLE: 11,756 participants from NHANES cohort.

OUTCOME MEASURES: Percentage of LBP reported.

METHODS: LBP reported in the 1999–2004 miscellaneous pain NHANES questionnaire was the dependent variable examined. Covariates included HbA1c, BMI, age, and family income ratio to poverty as continuous variables as well as race, gender, and smoking as binary variables. Individuals were further subdivided by weight class and diabetes status. Regression and graphical analyses were performed on the study population as a whole and also on subpopulations.

RESULTS: Increasing HbA1c did not increase the odds of reporting LBP in the full cohort. However, multivariate logistic regression of the 6 subpopulations revealed that the odds of LBP significantly increased with increasing HbA1c levels in normal weight diabetics. No other subpopulations reported significant relationships between LBP and HbA1c. LBP was also significantly associated with BMI for normal weight diabetics and also for obese subjects regardless of their DM status.

CONCLUSIONS: LBP is significantly related to DM status, but this relationship is complex and may interact with BMI. These results support the concept that LBP may be improved in normal weight diabetic subjects with improved glycemic control and weight loss, and that all obese LBP subjects may benefit from improved weight loss alone. © 2018 Elsevier Inc. All rights reserved.

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Introduction

Low back pain (LBP) is recognized as a leading cause of global disability and among the most common complaints presented to physicians [1]. The underlying etiology is complex and multifactorial with strong associations of LBP with age, obesity, genetics, physical activity, and intervertebral disc (IVD) degeneration [2,3]. The relationship between LBP and obesity is commonly thought to arise from alteration in the distribution of mechanical loads on the spine caused by obesity but likely also involves systemic inflammation and adipokines [2]. Obesity is the greatest risk factor for developing type 2 diabetes mellitus (DM) and also strongly correlates with IVD degeneration and back pain [3–6]. Although a complex relationship between obesity, DM, and LBP have been identified, the independent contribution of DM to LBP in obese and non-obese subjects remains unclear.

Diabetes mellitus is a complex disease that is associated with several clinically relevant spine pathologies including an increased incidence of intervertebral disc herniation and risk of spinal stenosis, as well as an increased odds of lumbar and cervical spine surgery complications [7–10]. Growing evidence from animal models reveals that DM can accelerate IVD degeneration [11,12]. However, in 2 human cohort studies of identical twins discordant for DM status there was no significant relationship between IVD degeneration and either type 1 or type 2 DM independent of obesity [13–16]. A recent large population study reported higher prevalence of chronic LBP in adults with DM, and these associations persisted after adjusting for commonly associated risk factors including obesity [17]. Both types 1 and 2 DM are characterized by elevated serum glucose, which is diagnosed clinically by measuring glycohemoglobin A1c (HbA1c). This study is designed to further parse out the relationships between LBP, DM, and BMI in a large adult cohort. We analyzed data from physical exam, laboratory, and questionnaires from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004, which included quantitative measurements of HbA1c and BMI.

Materials and methods

Study design

Data collection by NHANES was based on a complex sampling design, resulting in a nationally representative dataset of diverse ethnic and racial backgrounds aged between 20 and 85 years old. Our cohort was determined by anyone in NHANES 1999–2004 cohort with LBP measurements. Low back pain was the dependent variable examined and defined as answering affirmatively to the question: “During the last 3 months, did you have low back pain?”. Covariates included HbA1c, BMI, age, and family income

ratio to poverty as continuous variables as well as race, gender, and smoking as binary variables. Smoking status was defined as answering affirmatively to the question: “Have you smoked at least 100 cigarettes in your lifetime?”. Weight categories including obese, overweight, and normal weight were determined by the World Health Organization guidelines for interpreting BMI [18]. Diabetes status was determined using HbA1c $\geq 6.5\%$. Individuals were further subdivided by weight class and diabetes status into 6 subpopulations: normal weight diabetics, overweight diabetics, obese diabetics, normal weight nondiabetics, overweight nondiabetics, and obese nondiabetics.

Statistical analysis

Several covariates included in this study are thought to be correlated, such as BMI and HbA1c, therefore we performed a thorough exploration of multicollinearity in our analysis using variance inflation factors (VIFs). The VIF provides a quantitative metric for interpreting multicollinearity between covariates. The VIF values greater than 10 indicate significant multicollinearity that may influence estimates of the regression coefficients. The VIF calculated from the covariates in the entire study population are all less than 3, with the exception of the VIF calculated for 1 racial covariate, indicating negligible correlation between most covariates. For specific covariates in this dataset under scrutiny such as HbA1c and BMI VIF values are less than 1.5, and thus the assumption of covariate independence is statistically reasonable. Statistical significance was determined by $p < .05$. Regression and graphical analyses were performed on the study population as a whole and also on subpopulations. Regression was performed with the survey jackknife logistic regression command. Normal weight diabetics were divided into quartiles based on HbA1c level to assess odds of reporting LBP at different HbA1c levels. Analysis was performed with STATA version 13.1 software (StataCorp LLC, College Station, TX, USA) on demographic, laboratory, physical examination, and questionnaire data from NHANES. Sample weighting was performed in accordance with NHANES database user guidelines [19,20].

Results

The 11,756 subjects included in the model were subdivided by weight class and diabetes status. Of the subjects that were diabetic, 141 (1.2%) subjects were normal weight, 355 (3%) subjects were overweight, and 519 (4.4%) subjects were obese. Nondiabetic groups were comprised of 3,413 (29%) subjects that were normal weight, 3,910 (33%) subjects that were overweight, and 3,239 (27.6%) subjects that were obese (Table 1).

Analyses revealed reduced odds of reporting LBP was associated with gender, race, and poverty ratio whereas

Table 1
Descriptive statistics of subpopulations

	All	Diabetics			Nondiabetics		
		Normal weight	Overweight	Obese	Normal weight	Overweight	Obese
N	11,756	141 (1.2%)	355 (3%)	519 (4.4)	3,413 (29%)	3,910 (33%)	3,239 (27.6%)
Age (y) (SD)	49 (18.6)	64.5 (13.1)	64.5 (13.0)	58.6(13.2)	46.5 (20.0)	49.7 (18.5%)	47.3 (17.1)
BMI kg/m ² (SD)	28.3 (6.1)	22.9 (1.5)	27.6 (1.4)	36.3 (5.5)	22.5 (1.7)	27.3 (1.4)	35.1 (4.9)
HbA1c (SD)	5.5 (1.0)	8.6 (2.0)	8.2 (2.0)	8.1 (1.6)	5.2 (1.7)	5.3 (0.37)	5.4 (0.39)
HbA1c min	3.3	6.5	6.5	6.5	3.3	4	3.7
HbA1c max	14.3	14.3	14.3	14.7	6.4	6.4	6.4
Poverty ratio (SD)	2.6 (1.6)	2.0 (1.5)	2.2 (1.5)	2.3 (1.5)	2.6 (1.7)	2.7 (1.6)	3.0 (1.6)
Male	5,620 (48%)	85 (60%)	210 (59.2%)	242 (46.6%)	1581 (46.3%)	2136 (54.6%)	1304 (40%)
Mexican American	2,669 (23%)	46 (33%)	136 (38.3%)	195 (37.6%)	611 (17.9%)	951 (24.3%)	769 (24%)
Non-Hispanic White	6,005 (51%)	49 (35%)	117 (33.0%)	145(27.9%)	1964 (57.5%)	2027 (52%)	1542 (47.6%)
Non-Hispanic Black	2,141 (18.2%)	23 (16%)	67 (18.9%)	145(27.9%)	531 (15.6%)	613 (15.7%)	727 (22.4%)
Other races	411 (3.5%)	12 (8 %)	16 (4.8%)	12 (2.3%)	170 (5%)	115 (3%)	78 (2.4 %)
Smoking	5,796 (49%)	79 (56%)	195 (55%)	277 (53.4)	1691 (49.5%)	1962 (50%)	1494 (46%)
LBP reported	4,526 (38.5%)	41 (29%)	136 (38.3%)	231 (44.5%)	1169 (34.2%)	1480 (37.9%)	1400 (43.2%)

Note: SD, standard deviation.

increased odds of reporting LBP was associated with smoking status and BMI (Table 2).

Odds of reporting LBP increase with elevated HbA1c

The odds of reporting LBP do not significantly increase with HbA1c levels (OR 1.02± 0.04, p=.17) in the 11,756 subjects included in the NHANES cohort of participants from 1999 to 2004 (Table 2). However, multivariate logistic regression of the 6 subpopulations revealed that the odds of reporting LBP statistically, significantly increased with HbA1c levels in normal weight diabetics (OR 1.59±.43, p=.01) (Table 3). The Figure illustrates how normal weight diabetics (18.5 < BMI < 25, HbA1c ≥6.5%, n=141) tend to show an increasing proportion of reported LBP as HbA1c increases by quartile. No other subpopulations showed significant relationships between LBP and HbA1c.

Odds of reporting LBP increase with BMI

Increasing BMI increased the odds of reporting LBP among the full study cohort (OR 1.03±0.01, p < .001). The

LBP was also significantly associated with BMI for both normal weight diabetics (OR 1.66±0.55, p=.016) and for obese subjects with (OR 1.05±0.43, p=.017) and without (OR 1.03±0.23, p=.001) DM.

Odds of reporting LBP increase with subject demographic factors

Multivariate logistic regression revealed many demographic factors associated with both an increase and decrease in reporting LBP (Table 4).

Poverty ratio was inversely associated with LBP in normal weight diabetics (OR 0.65±0.10, p=.01), as well as nondiabetics of all weight classes, whereas smoking was directly associated with LBP in this same subgroup (OR 1.59±0.24, p=.01). Smoking also increased odds of reporting LBP in overweight diabetics, (OR 3.09±0.86, p < .001).

Race played a role in reporting LBP among nondiabetic subjects. Mexican American overweight (OR 0.65±0.12, p=.03) and obese (OR 0.61±0.13, p=.03) nondiabetics had decreased odds of reporting LBP. Similar findings were seen in overweight (OR 0.72±0.12, p=.05) and obese (OR 0.55±0.12, p=.01) nondiabetics of Non-Hispanic Black

Table 2
Multivariate analysis of patient demographics with LBP for the entire NHANES population

	1999–2004	
	Odds ratio	p value
Age	1.00±0.01	.96
BMI	1.03±0.01	< .001
HbA1c	1.02±0.04	.17
Poverty ratio	0.89±0.02	.01
Male	0.85±0.03	< .001
Mexican American	0.69±0.07	< .001
Non-Hispanic White	1.03±0.12	.80
Non-Hispanic Black	0.76±0.61	.01
Other races	0.76±0.13	.11
Smoker	1.39±0.07	< .001

Table 3
Multivariate analysis of HbA1c and BMI with LBP for 6 subpopulations

		HbA1c (OR/p value)	BMI (OR/p value)
Diabetic	All patients	1.02±.04/p=.17	1.03±0.01/p < .001
	Normal weight	1.59±0.43/p=.01	1.66±0.55/p=.02
	Overweight	0.93±0.18/p=.55	1.06±0.22/p=.59
Nondiabetic	Obese	0.94±0.15/p=.50	1.05±0.43/p=.02
	Normal weight	0.88±0.26/p=.47	1.03±0.57/p=.20
	Overweight	1.23±0.34/p=.20	1.01±0.05/p=.83
	Obese	0.97±0.44/p=.83	1.03±0.23/p=.01

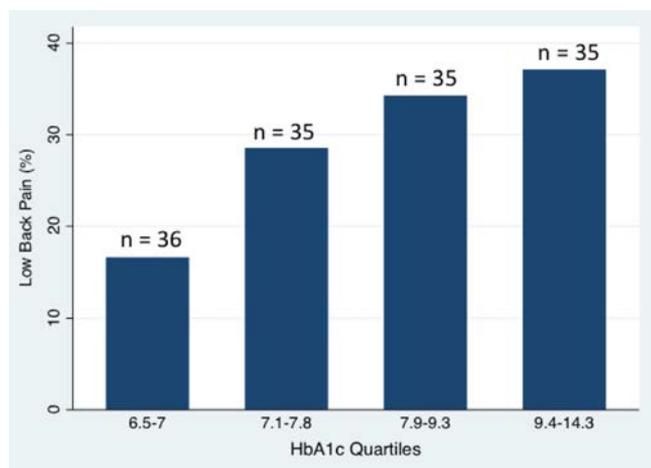


Fig. HbA1c was divided into quartiles for normal weight diabetics. Graphical analysis of percent low back pain reported by HbA1c quartile in normal weight and diabetic subjects (BMI between 18 and 25, HbA1c ≥ 6.5) subjects. As HbA1c increases, there is a trend toward increase in the percent of survey participants reporting low back pain per quartile.

backgrounds. Finally, similar to the diabetic subpopulations, smoking was found to independently increase odds of reporting LBP in overweight (OR 1.43 \pm 0.12, $p < .001$) and obese (OR 1.30 \pm 0.10, $p=.002$) nondiabetics.

Discussion

This study assessed the odds of reporting LBP among 6 subpopulations stratified by DM and obesity status using a population-based NHANES survey that simultaneously assessed for other risk factors of LBP. This study builds on previous work linking DM to LBP by using NHANES database of a different cohort than previously investigated [17],

and extending this relationship in normal weight, overweight, and obese populations. The analyses showed 2 important findings: (1) normal weight DM participants had significantly increased odds of reporting LBP with both increasing HbA1c and BMI levels as independent factors; and (2) obese participants regardless of their DM status had increased likelihood of reporting LBP.

Normal weight DM participants had significantly increased odds of reporting LBP with increasing HbA1c levels, indicating that poorly controlled hyperglycemia may contribute to LBP independent of BMI. The BMI was also significantly associated with reporting LBP. Together, these findings suggest a strategy to improve LBP in normal weight diabetics by focusing both on glycemic control and weight loss, even for individuals at their target BMI. A relationship between HbA1c and LBP in overweight and obese DM participants was not identified. There are 2 possible explanations for this: (1) the obesity relationship dominated the association with HbA1c in these patients, or (2) obese DM participants may have other more severe health conditions that have a greater association on LBP. HbA1c and other markers of DM disease progression have been previously implicated in reporting of LBP. These epidemiological observations in conjunction with the current study corroborates animal studies linking chronic high blood sugar to hyperglycemia-related tissue changes, and together these findings may eventually inform new LBP treatment or management strategies.

A significant relationship between LBP and BMI was also identified in the entire cohort, a result that has been previously reported highlighting the need to reduce body weight in all LBP patients [21,22]. The connection between LBP and obesity however remains nuanced. A previous study in a cohort of 2,599 Southern Chinese volunteers

Table 4
Multivariate analysis of patient demographics with LBP for diabetic and nondiabetic subjects

	Diabetics					
	Normal weight		Overweight		Obese	
	Odds ratio	p value	Odds ratio	p value	Odds ratio	p value
Age	1.00 \pm 0.02	.98	0.99 \pm 0.01	.39	0.99 \pm 0.01	.23
Poverty ratio	0.65 \pm 0.10	.01	0.88 \pm 0.12	.37	0.92 \pm 0.11	.48
Male	2.03 \pm 1.31	.28	0.38 \pm 0.20	.07	0.62 \pm 0.18	.10
Mexican American	1.13 \pm 1.24	.91	0.61 \pm 0.39	.44	0.70 \pm 0.49	.61
Non-Hispanic White	4.05 \pm 4.63	.23	0.88 \pm 0.56	.84	1.40 \pm 1.04	.65
Non-Hispanic Black	0.84 \pm 1.12	.90	0.76 \pm 0.34	.54	0.96 \pm 0.71	.95
Other races	1.81 \pm 1.00	.30	0.86 \pm 0.61	.83	1.09 \pm 1.09	.94
Smoker	1.59 \pm 0.24	.01	3.09 \pm 0.86	< .001	1.69 \pm 0.59	.15
	Nondiabetics					
Age	1.00 \pm 0.00	.77	1.00 \pm 0.00	.78	1.00 \pm 0.00	.45
Poverty ratio	0.89 \pm 0.03	.002	0.91 \pm 0.03	.01	0.86 \pm 0.02	< .001
Male	0.97 \pm 0.08	.75	0.88 \pm 0.05	.05	0.80 \pm 0.06	.01
Mexican American	0.74 \pm 0.16	.18	0.65 \pm 0.12	.03	0.61 \pm 0.13	.03
Non-Hispanic White	1.24 \pm 0.20	.18	1.02 \pm 0.17	.89	0.76 \pm 0.16	.20
Non-Hispanic Black	0.95 \pm 0.19	.78	0.72 \pm 0.12	.05	0.55 \pm 0.12	.01
Other races	0.67 \pm 0.17	.13	0.83 \pm 0.20	.45	0.80 \pm 0.31	.56
Smoker	1.17 \pm 0.11	.10	1.43 \pm 0.12	< .001	1.30 \pm 0.10	.01

showed that elevated BMI values, specifically those associated with being overweight or obese, were significantly associated with IVD degeneration [5]. However these findings contrasted with a study of 44 monozygotic male twins, where it was concluded that greater BMI was not associated with disc degeneration [15]. Moreover, another study of male monozygotic twins found no relationship between obesity and prevalence of LBP or seeking care for LBP [14].

Smoking significantly increased odds of reporting LBP by 1% to 3%. Previous studies have also shown significant associations between LBP rates and smoking. The relationship between smoking and LBP has been previously shown and may be dose-dependent [23]. However, the underlying etiology for smoking-associated LBP is still contested. Some research pointed to the frequency and intensity of smoking leading to LBP, although others have found people who smoke are more likely to report LBP [24,25]. Thus the arrow of causality has yet to be defined.

Being of Mexican American or Non-Hispanic Black descent and living below the poverty line appeared to be protective for LBP in several nondiabetic subgroups. This could be in part caused by the survey strategy of NHANES, but is possibly caused by a phenomenon described in previous works as the “Immigrant paradox” or “Hispanic Paradox” which postulates migrants to the United States from Mexico often report better health outcomes than US residents [26]. For Non-Hispanic Blacks, this association may be linked to a long history of disparities in treatment for LBP, perhaps making blacks less likely to report LBP when surveyed [27–29].

Defining an exact mechanism for how HbA1c may affect LBP is outside of the scope of this study, yet one proposed mechanism points to accumulation of advanced glycation endproducts (AGEs) resulting in accelerated spinal degeneration. AGEs are prooxidant metabolic derivatives of non-enzymatic reactions between reducing sugars and free amines of proteins, that form in increased abundance under diabetic conditions with high levels of HbA1c [30]. Extracellular and intracellular AGE precursors are highly reactive and permanently alter connective tissue proteins, plasma lipoproteins, cell membrane phospholipids, and DNA to modulate several prooxidant effects influencing inflammation, cell proliferation, apoptosis, and insulin signaling. The AGEs as a mechanism for spinal degeneration are supported by animal models with controlled dietary and diabetic interventions that demonstrated a relationship between spinal tissue AGE content and diabetes-induced spinal pathology where treatment including an anti-AGE drug reduced that spinal pathology [11,12]. Furthermore, animals fed diets high in AGE also demonstrated increased spinal pathology independent of obesity or diabetic conditions [31,32]. Accumulation of AGEs in spinal tissues can drive changes to cells and collagenous tissues and nonenzymatic glycation of the IVD is known to result in altered T2 magnetic resonance imaging signals and increased stiffness

and brittleness in IVD tissue biomechanical behaviors [12,32–36].

The exact effects of obesity on back pain and disc degeneration are also complex. Obese conditions are similarly known to be highly proinflammatory in addition to altering spinal biomechanics to predispose to overloading and injurious conditions. Research has linked greater fat composition with more disability and greater intensity of low back pain [37]. Upregulation of adipokines in adipose tissue is thought to cause oxidative stress in vertebral tissues by creating proinflammatory conditions [2]. The scientific literature is therefore consistent with the concept that high systemic HbA1c and obese conditions can result in increased spinal degeneration as a potential cause back pain, yet it is important to highlight that such mechanisms need further investigation with mechanistic and interventional studies. Furthermore, associations between obesity and DM with pain or spinal degeneration observed in this study and others in humans (and even controlled animal studies) involve complex interactions with multiple systemic conditions, overall health, and activity levels that may also predispose to painful conditions.

Limitations

A limitation of this study is that the NHANES sample does not include measures of IVD degeneration. Additionally, BMI does not distinguish between individuals with increased lean muscle mass vs. adiposity, therefore anthropometric measures indicative of body composition, such as waist circumference, should be included in future work.

Consequently, prospective clinical and basic science studies are required to further parse out the role of HbA1c in LBP etiology and progression. Additionally, the NHANES database does not specify if respondents had Type I or Type II DM, and although elevated HbA1c defines both types of DM, the etiology of LBP could occur differently and also depend on how long respondents have had their condition. Finally, this study asked if LBP occurred in the last 3 months, but did not identify the timing of when the LBP occurred. Future studies should be designed with a more specific screening question for chronic LBP.

Conclusion

We conclude that LBP is related to DM status, but this relationship is complex and may interact with BMI. This study showed that the odds of reporting LBP increased with HbA1c independent of BMI in nonobese, nonoverweight diabetics and increased with BMI in obese diabetic and nondiabetic subjects. Together, results suggest that glycemic control may be an important management tool to reduce LBP in DM patients particularly for those who are not obese and that weight reduction may help reduce LBP prevalence in all patients regardless of DM status. Additional clinical and basic science studies are required to

elucidate how HbA1c contributes to the etiology and progression of LBP.

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