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Elevated Glycohemoglobin HbA1c is Associated with Low Back Pain in Non-Overweight 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 BMI in a large cohort of adult survey participants.

Study Design/Setting—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 six subpopulations: normal weight (BMI 18.5-25), overweight (BMI: 25-30), and obese (BMI >30) diabetics and non-diabetics. Diabetes was defined with glycohemoglobin A1c (HbA1c) ≥ 6.5%.

Patient Sample—11,756 participants from NHANES cohort.

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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.

Conclusion—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.

Keywords

Low back pain; diabetes mellitus; obesity

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 degeneration (IVD).^{2,3} The relationship between LBP and obesity is commonly thought to arise from alteration in the distribution of mechanical loads on the spine due to 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 intervertebral disc degeneration and back pain.^{4,5,3,6} While the relationships between obesity and DM, and obesity and LBP have been well described, the independent contribution of DM to LBP in obese and non-obese subjects remains unclear.

DM 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 intervertebral disc degeneration.^{11,12} However, in two human cohort studies of identical twins discordant for DM status there was no significant relationship between IVD 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 1999-2004 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 20-85 years old. Our cohort was determined by anyone in NHANES 1999-2004 cohort with LBP measurements. LBP 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 non-diabetics, overweight non-diabetics, and obese non-diabetics.

Statistical Analysis

Several covariates included in this study are thought to be correlated, such as BMI and HbA1c, so therefore we performed a thorough exploration of multicollinearity in our analysis using variance inflation factors (VIF). The VIF provides a quantitative metric for interpreting multicollinearity between covariates. 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 one racial covariate, indicating negligible correlation between most covariates. For specific covariates in this data set 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 $p < 0.05$. 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 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 then 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. Non-diabetics had 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).

The univariate analyses found reduced odds of reporting LBP was associated with gender, race, and poverty ratio while increased odds of reporting LBP was associated with smoking status and BMI (Table 2).

Odds of Reporting LBP Increased with Elevated HbA1c

Increasing HbA1c did not significantly increase the odds of reporting LBP (OR 1.02± 0.04, p=0.17) in the 11,756 subjects included in the NHANES cohort of participants from 1999-2004 (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=0.01) (Table 3). A graphical trend analysis of this cohort assessing HbA1c levels by quartile further revealed that these normal weight diabetics tended to show (18.5 < BMI < 25, HbA1c < 6.5%, n=141) increasing proportion of reported LBP with increasing HbA1c levels (Figure 1). No other subpopulations reported significant relationships between LBP and HbA1c.

Odds of Reporting LBP Increased with BMI

Increasing BMI increased the odds of reporting LBP among the full study cohort (OR 1.03±0.01, p<0.001). LBP was also significantly associated with BMI for both normal weight diabetics (OR 1.66±0.55, p=0.016) and for obese subjects with (OR 1.05±0.43, p=0.017) and without (OR 1.03±0.23, p=0.001) DM.

Odds of Reporting LBP Increased 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=0.01), as well as non-diabetics of all weight classes, while smoking was directly associated with LBP in this same subgroup (OR 1.59±0.24, p=0.01). Smoking also increased odds of reporting LBP in overweight diabetics, (OR 3.09±0.86, p<0.001).

Race played a role in reporting LBP among non-diabetic subjects. Mexican American overweight (OR 0.65±0.12, p=0.03) and obese (OR 0.61±0.13, p=0.03) non-diabetics had decreased odds of reporting LBP. Similar findings were seen in overweight (OR 0.72±0.12, p=0.05) and obese (OR 0.55±0.12, p=0.01) non-diabetics of Non Hispanic Black backgrounds. Finally, similar to the diabetic subpopulations, smoking was found to independently increase odds of reporting LBP in overweight (OR 1.43±0.12, p<0.001) and obese (OR 1.30±0.10, p=0.002) non-diabetics.

DISCUSSION

This study assessed the odds of reporting LBP among six 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 two 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. 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 two 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, and 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 showed that elevated BMI values, specifically those associated with being overweight or obese, were significantly associated with intervertebral disc 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 1-3%. Previous researchers have also found 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 while 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 non-diabetic subgroups. This could be in part due to the survey strategy of NHANES, but is possibly do with a phenomenon described in previous works as the “Immigrant paradox” or “Hispanic Paradox” which postulates migrants to the US 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}

An exact mechanism for how HbA1c may affect LBP remains impossible to determine from this study, yet one proposed mechanism points to accumulation of advanced glycation endproducts (AGEs) resulting in accelerated spinal degeneration. AGEs are pro-oxidant metabolic derivatives of nonenzymatic 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 pro-oxidant effects influencing inflammation, cell proliferation, apoptosis and insulin signaling. 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 non-enzymatic glycation of the IVD is known to result in altered T2 MRI 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 pro-inflammatory 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 and 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 versus 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 while elevated HbA1c defines both types of DM, the etiology of low back pain could occur differently and also depend on how long respondents have had their condition. Finally, this study asked if LBP occurred in

the last three 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 non-obese, non-overweight diabetics and increased with BMI in obese diabetic and non-diabetic 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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Figure 1. 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 (BMI between 18 and 25, HbA1c ≥ 6.5) subjects. As HbA1c increases, there is a trend towards increase in the percent of survey participants reporting low back pain per quartile.

Table 1

Descriptive Statistics of Subpopulations

	All	Diabetics			Non-Diabetics		
		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 years (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 Race	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%)

Table 2

Univariate Analysis of entire NHANES population

	1999-2004	
	Odds Ratio	P- value
Age	1.00+ 0.01	0.96
BMI	1.03+ 0.01	<0.001
HbA1c	1.02+ 0.04	0.17
Poverty Ratio	0.89+ 0.02	0.01
Male	0.85+0.03	<0.001
Mexican American	0.69+ 0.07	<0.001
Non Hispanic White	1.03+ 0.12	0.80
Non Hispanic Black	0.76+ 0.61	0.01
Other Race	0.76+ 0.13	0.11
Smoker	1.39+ 0.07	<0.001

Table 3

Multivariate Analysis of HbA1c and BMI associated with LBP

		HbA1c (OR/P-value)	BMI (OR/P-value)
All Patients		1.02 + .04 / p=0.17	1.03+ 0.01 / p<0.001
Diabetic	Normal Weight	1.59 + 0.43 / p=0.01	1.66+ 0.55 / p=0.02
	Overweight	0.93 + 0.18 / p=0.55	1.06+0.22 / p=0.59
	Obese	0.94 + 0.15 / p=0.50	1.05+0.43 / p=0.02
Non-Diabetic	Normal Weight	0.88+ 0.26 / p=0.47	1.03+ 0.57 / p=0.20
	Overweight	1.23+ 0.34 / p=0.20	1.01+ 0.05 / p=0.83
	Obese	0.97+ 0.44 / p=0.83	1.03+ 0.23 / p=0.01

Controlling for age, gender, race, and gender

Table 4

Multivariate Analysis of Patient Demographics and LBP

Diabetics						
	Normal Weight		Overweight		Obese	
	Odds Ratio	P-value	Odds Ratio	P-value	Odds Ratio	P-value
Age	1.00+ 0.02	0.98	0.99+0.01	0.39	0.99+0.01	0.23
Poverty Ratio	0.65+ 0.10	0.01	0.88+0.12	0.37	0.92+0.11	0.48
Male	2.03+1.31	0.28	0.38+0.20	0.07	0.62+0.18	0.10
Mexican American	1.13+ 1.24	0.91	0.61+0.39	0.44	0.70+0.49	0.61
Non Hispanic White	4.05+ 4.63	0.23	0.88+0.56	0.84	1.40+1.04	0.65
Non Hispanic Black	0.84+ 1.12	0.90	0.76+0.34	0.54	0.96+0.71	0.95
Other Race	1.81+ 1.00	0.30	0.86+0.61	0.83	1.09+1.09	0.94
Smoker	1.59+ 0.24	0.01	3.09+0.86	<0.001	1.69+0.59	0.15
Non-Diabetics						
Age	1.00+0.00	0.77	1.00+0.00	0.78	1.00+0.00	0.45
Poverty Ratio	0.89+0.03	0.002	0.91+0.03	0.01	0.86+0.02	<0.001
Male	0.97+0.08	0.75	0.88+0.05	0.05	0.80+0.06	0.01
Mexican American	0.74+0.16	0.18	0.65+0.12	0.03	0.61+0.13	0.03
Non Hispanic White	1.24+0.20	0.18	1.02+0.17	0.89	0.76+0.16	0.20
Non Hispanic Black	0.95+0.19	0.78	0.72+0.12	0.05	0.55+0.12	0.01
Other Race	0.67+0.17	0.13	0.83+0.20	0.45	0.80+0.31	0.56
Smoker	1.17+0.11	0.10	1.43+0.12	<0.001	1.30+0.10	0.01