THE INFLUNCE OF DIABETES MEDICATIONS ON THE ASSOCIATIONS BETWEEN BMI AND CARDIOVASCULAR HEALTH RISKS

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Abstract

The purpose was to observe the influence of diabetes medications on the association between body mass index (BMI) and cardiovascular health (CVH). Individuals with type 2 diabetes (T2D) from the National Health and Nutrition Examination Survey (NHANES Continuous 1999-2018) were grouped by diabetes medications with similar body weight side effects. There was a positive association between BMI for triglycerides in the combination medications group ($P<0.002$). Conversely, there were negative associations between BMI for HbA1c in the weight gain medications group ($P=0.02$), and total cholesterol in the weight loss and weight gain medication groups ($P<0.05$). Finally, no associations were between BMI in any medication group for fasting glucose, blood pressure or high-density lipoproteins ($P>0.05$). Therefore, T2D medications may weaken or invert the commonly observed association between obesity and CVH. Thus, patients living with T2D and obesity may have better CVH compared to patients without obesity taking the same T2D medication.

Acknowledgement

I would first like to thank my parents for supporting and encouraging me on this long journey. You both were there for me through the hardships of my university studies and made sure I would stay focused on what is important. My sister, who would tell me the truth even when I didn’t want to hear it. Thank you for being there for me when I needed you most and motivating me when I over exaggerated my problems. I hope I was able to make you all proud of the person I have become and the path I chose to pursue.

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Table of Contents

List of Tables

List of Figure

List of Abbreviations

Abbreviation	Term
BMI	Body Mass Index
CombMed	Combination Medications
DBP	Diastolic Blood Pressure
DPP	Dipeptidyl peptidase
GLP	Glucagon-like peptide
HbA1c	Hemoglobin A1c
HDL	High Density Lipoproteins
NHANES	National Health and Nutrition Examination Survey
nOB	No Obesity
OB	Obesity
OGTT	Oral Glucose Tolerance Test
SBP	Systolic Blood Pressure
SGLT	Sodium Glucose Co-Transporter
T2D	Type 2 Diabetes
TZD	Thiazolidinediones

U.S.	United States
WgMed	Weight Gain Medications
WlMed	Weight Loss Medications
WnMed	Weight Neutral Medications

1.0 General Introduction

The prevalence of obesity in United States (U.S.) adults has escalated in the past few decades from 15% in 1980 (1) to 42% in 2017 (2). Obesity is well known to be associated with developing further health complications, including type 2 diabetes (T2D) (3–5). T2D is a major chronic disease, which as of 2018 is prevalent in over 34 million U.S. adults, affecting an estimated 13% of the U.S. population (6). In 2017, 25% of all U.S. healthcare expenditures went towards diabetes care (7). Those living with T2D are advised to lower their blood glucose and glycated hemoglobin (HbA1c) levels through lifestyle management, along with antidiabetic medications (8).

Medications are effective interventions for lowering HbA1c and blood glucose levels (9). Diabetes medication work through several different physiological mechanisms and can have side effects that result in body weight gain or loss (10). However, it is unknown if diabetes medications alter the known association between BMI and other cardiovascular risk factors. Thus, the purpose of this study was to examine the potential influence diabetes medications have on the relationship between BMI and cardiovascular health risks.

2.0 Review of Literature

2.1 Introduction

Obesity is a condition that increases the risk of developing further health complications (5). One of the major health complications associated with obesity is T2D which is characterized by hyperglycemia as a result of complete or partial insufficiency of insulin secretion and/or action (11,12). T2D is the most prevalent type of diabetes accounting for 8.5% of US adult population (13).

This literature review will discuss T2D, the importance of regulating blood glucose and HbA1c, obesity and the cardiovascular health risks associated with obesity. This review will also outline the medications currently available for T2D patients and considerations when prescribing medications to individuals living with obesity.

2.2 Type 2 Diabetes (T2D)

T2D is characterized by the inability to control blood glucose levels due to beta cell dysfunction and/or insulin resistance (14). T2D is diagnosed as: an HbA1c $\geq$ 6.5%, a fasting glucose $\geq$ 7 mmol/L, a randomized blood glucose test $\geq$ 11.1 mmol/L or a two hour oral glucose tolerance test (OGTT) $\geq$ 11.1 mmol/L (11). Early symptoms for T2D include excessive urination, excessive thirst, increased hunger, and fatigue (15). Longer term complications can include CVD, vision changes, yeast infections, slow healing sores, and feelings of numbness in peripheral body parts (16).

2.3 Managing Blood Glucose and HbA1c

Individuals with T2D usually have elevated blood glucose levels which is known as hyperglycemia. Hyperglycemia can lead to damage of capillary endothelial cells in the retina, mesangial cells in the renal glomerulus, and Schwann cells in peripheral nerves (17). Blood glucose can be difficult to regulate, however regular self-monitoring with the use of a glucometer makes self-management easier for the individual. HbA1c or glycated hemoglobin is a molecule formed when glucose binds with the proteins on red blood cells (18). Higher blood glucose levels increase the likelihood for glucose to bind with these proteins. Testing HbA1c is the gold standard when looking at T2D blood glucose control and indicates blood glucose levels over a 2-3 month period (19).

2.4 Obesity

Obesity is defined as an excessive amount of body fat that has negative implications on one's health (20). The most common measure used to diagnose obesity is body mass index (BMI). BMI is calculated by dividing an individual's body weight in kilograms from their height in meters squared (kg/m^2). It has been well established that a BMI $\geq$ 30 kg/m^2 indicates a person is living with obesity (4). Health quality of life such as overall physical functioning and mobility is greatly increased with reductions in body weight (22).

2.5 Obesity and Cardiovascular Health Risks

Individuals living with obesity are shown to have elevated health risks compared to those without obesity (23). It is well established that blood glucose and HbA1c levels are more likely to be elevated for individuals living with obesity as they are at increased risk for insulin resistance (24). Obesity is also associated with hypertension which is defined as blood pressure measures $\geq$140/90 mmHg (25) and dyslipidemia or abnormally high cholesterol levels which is defined as triglycerides $\geq$150mg/dl or HDL < 40 mg/dl) (26–28).

2.6 Medications Available for Treatment of T2D

Antidiabetic medications in conjunction with lifestyle are a vital part of treatment for individuals with diabetes in order to control glucose levels (9). These medications work through a number of pathways and have varied effects on body weight. Amylin analogs, and insulin are currently only effective as subcutaneous injections as they are destroyed by gastric acid before reaching the bloodstream (29,30). Glucagon-like peptide (GLP)-1-agonists are also only injectable however recent discoveries in oral options effectively lower blood glucose (31). Biguanides, sodium glucose co-transporters type 2 (SGLT2) inhibitors, alpha-glucosidase inhibitors, dipeptidyl peptidase (DPP)-4-inhibitors , sulfonylureas, meglitinides, and thiazolidinediones are all oral medication options currently available to lower blood glucose (10,32).The medications examined in this paper include the following: amylin analogs, biguanides, GLP-1-agonists, SGLT2 inhibitors, alpha-glucosidase inhibitors, DPP-4-inhibitors, insulin, sulfonylureas, meglitinides, and thiazolidinediones.

Medications Associated with Weight Loss

The following T2D medications are associated with a decrease in body weight: amylin analogs, biguanides, GLP-1-agonists and sodium glucose co-transporters type 2 (SGLT2) inhibitors (10,33–38).

Amylin Analogs

The only available amylin medication is known as pramlintide which is a synthetic compound of the hormone amylin (10). Human amylin is co-secreted with insulin after eating a meal which lowers glucose in the bloodstream (39). Pramlintide and amylin lower blood glucose by suppressing postprandial production of glucose and slowing the rate of gastric emptying

(10,33). Currently the mechanism behind weight loss is unknown but could be attributed to reductions in food intake as feelings of satiety after a meal are increased (40).

Biguanides

The most commonly used medication for T2D is metformin as it is associated with minimal negative side effects and potential improvements to cardiovascular health (11). Metformin reduces blood glucose concentration by lowering glucose production from the liver and increasing insulin sensitivity (35). The mechanism causing weight loss with metformin is thought to be associated with decreased appetite (41).

GLP-1-agonists

GLP-1 is a gut hormone which is secreted by the intestines after eating as a meal in response to increased glucose levels (42). GLP-1-agonists are medications which bind to G-protein receptors similarly to the gut hormone GLP-1. These medications lower blood glucose by increasing insulin secretion from the pancreas and inhibiting glucose production from the liver (14,34,42). Reduction in body weight may be associated with decreased gastric emptying and increases feelings of satiety (43).

SGLT2 Inhibitors

SGLT2 inhibitors lower blood glucose concentrations by increasing urinary glucose elimination and reducing renal glucose re-absorption after a meal. (44). Long term use of dapagliflozin is reported to be associated with statistically significant weight loss through reductions of visceral adipose tissue and subcutaneous adipose tissue (45). Another study demonstrates that empagliflozin is associated with a shift usage from sugars to fats for energy which may explain the reduced body weight over time (46).

Medications Associated with Neutral Changes in Body Weight

The following medications are reported to be weight neutral: alpha-glucosidase inhibitors and Dipeptidyl peptidase (DPP)-4-inhibitors (10,47,48).

Alpha-glucosidase Inhibitors

Alpha glucosidase inhibitors prevent the enzyme alpha-glucosidase for breaking down complex sugars into simple sugars (12,49). By inhibiting alpha glucosidase, the small intestine is limited to the absorption of complex sugars which lowers the rise in blood glucose levels after eating.

DPP-4-inhibitors

DPP-4-inhibitors extend the half-life of endogenous and exogenous GLP-1 by reducing the actions of DPP-4 enzymes (50). Extending the actions of GLP-1 lower blood glucose levels through the prolonged release of insulin. The use of DPP-4 inhibitors are weight neutral compared to GLP-1-agonists, indicating lower GLP-1 receptor stimulation or lower release of GLP-1 (50,51).

Medications Associated with Weight Gain

The following medications are associated with a clinically significant increase in body weight (i.e. >5-10%): insulin, sulfonylureas, meglitinides, and thiazolidinediones (TZD) (10,52–56).

Insulin

Exogenous insulin is recommended for T2D patients when oral antidiabetic agents fail to manage blood glucose levels (57). Insulin suppresses hepatic glucose production and increases glucose uptake by adipose and muscle tissues to decrease blood glucose levels (34). Higher levels of insulin increases stimulation of lipogenesis which could result in weight gain (58).

Sulfonylureas and Meglitinides

Sulfonylureas and meglitinides both induce closure of the potassium ATP channels in beta cells which promotes insulin secretion (53,59). Promoting short term rapid insulin secretion aids in the absorption of glucose after a meal therefore lowering blood glucose. Meglitinides have a shorter half-life which is why they are less likely to cause hypoglycemia compared to sulfonylureas. (60,61). As seen with patients on exogenous insulin therapy, individuals on these medications also gain weight.

TZDs

TZDs lower blood glucose level by increasing insulin sensitivity in skeletal muscle (55). Use of TZDs are associated with weight gain resulting from accumulations of subcutaneous fat (62). These medications may also cause fluid retention (i.e. body water) in peripheral tissues which can lead to swelling and weight gain (55).

Antidiabetic Combinations

Combination medications are used as a progressive measure when individuals are unable to maintain adequate blood glucose control with a single medication. When prescribing oral combinations, one medication generally increase insulin sensitivity while the other increase secretion of insulin (63). Metformin and sulfonylureas are usually the first medications packaged followed by thiazolidinediones or alpha-glucosidase inhibitors (64,65).

Summary of Literature

It is well known that obesity is associated with higher health risk along with increased risk for the development of T2D. Those living with T2D may be prescribed medications with weight altering effects which may change the commonly observed associations between obesity and cardiovascular health risks. The aim of this study is to examine if diabetes medications alter the associations between BMI and CVH.

3.0 Manuscript

3.1 Abstract

The purpose was to observe the influence of diabetes medications on the association between body mass index (BMI) and cardiovascular health (CVH). Individuals with type 2 diabetes (T2D) from the National Health and Nutrition Examination Survey (NHANES Continuous 1999-2018) were grouped by diabetes medications with similar body weight side effects. There was a positive association between BMI for triglycerides in the combination medications group ($P<0.002$). Conversely, there were negative associations between BMI for HbA1c in the weight gain medications group ($P=0.02$), and total cholesterol in the weight loss and weight gain medication groups ($P<0.05$). Finally, no associations were between BMI in any medication group for fasting glucose, blood pressure or high-density lipoproteins ($P>0.05$). Therefore, T2D medications may weaken or invert the commonly observed association between obesity and CVH. Thus, patients living with T2D and obesity may have better CVH compared to patients without obesity taking the same T2D medication.

3.2 Introduction

Obesity and T2D both lead to severe health outcomes. The use of various anti-hyperglycemic medications are effective in lowering blood glucose levels though different mechanisms, with some promoting weight gain or weight loss. However, the effects these medications for T2D have on the health of individuals independent of BMI is still not fully understood. Therefore, the objective of this study is to examine the influence anti-hyperglycemic medications may have on the associations between BMI and cardiovascular health risk.

3.3 Methods

Participants

The data in this study was collected by the National Health and Nutrition Examination Survey (NHANES) Continuous 1999 - 2018 (n= 101 316). NHANES is a nationally represented survey in the Unites states conducted every 2 years focusing on a wide range of different health topics (66). The survey data for NHANES is collected through home interviews, followed by a health examination and laboratory samples which are conducted in mobile medical examination centers (MEC). In the home interviews, participants are asked demographic, socioeconomic and health related questions. During the health examinations, medical, dental and physiological measurements are taken. Furthermore, laboratory samples are taken by trained medical personnel. All participants gave written informed consent before participating.

Participants for this study were included if they had diabetes as defined by the following criteria: were told by a doctor they have diabetes (n= 6807), fasting glucose >=7 mmol/L (n= 2587), random blood glucose $\geq$ 11.1 mmol/L (n= 783), HbA1c level $\geq$ 6.5% (n = 5578), currently on a diabetes prescription medication (n =6011), or 2-hour glucose tolerance test $\geq$ 11.1 mmol/L (n =810). Individuals were excluded if they had missing data for body weight (n= 6134), height (n= 13 077), or HbA1c (n= 36 364). Individuals were also excluded if they were only taking insulin (n= 517), age < 20 years (n= 46 235), or answered “yes” to the question “Are you pregnant?” (n= 1722). An analytical sample of 7953 were used for the final analysis. Outliers for each cardiovascular health risk were excluded for each relevant analysis: (HbA1c n = 3, SBP n = 1, DBP n = 1, total cholesterol n = 4, HDL n = 2, Triglyceride n = 4). BMI was stratified into two groups: no obesity (nOB, BMI < 30 kg/m^2) and obesity (OB, BMI $\geq$ 30 kg/m^2).

Interview and Examination Measures

Demographic information was collected though home interviews and questionnaires prior to the health examination in the MEC. Sex was recorded as male or female. Individuals older than 85 years of age were recoded as 85 years of age for disclosure reasons. Ethnicity was re-coded as either Non-Hispanic White or Other Race/Multi-Racial. All body measurements were conducted by trained professional in the MEC. Body weight was measured using a digital scale. Standing height was measured using a stadiometer with a fixed backboard and an adjustable head piece. BMI was calculated as body weight (kg) and divided by height squared (m^2) (67). Waist circumference was measured in centimeters at the level of the uppermost lateral border of the right ilium (68).

For smoking status, individuals were asked if they smoked at least 100 cigarettes in their lifetime. If they answered "no" they were classified as nonsmokers. If they answered "yes" they were then asked how often they currently smoke cigarettes in a month. If participants answered "every day" or "some days" they were classified as current smokers. If participants answered "not at all", "refused", "don't know" or had missing data, they were classified as a past smoker.

Socioeconomic status of participants was determined using the poverty income ratio (PIR). The Department of Health and Human Services' (HHS) poverty guidelines were used as the poverty measure to calculate this index. The values were calculated by dividing the family income by the poverty guidelines for the specific amount of family members set by year and state. Individuals who had values greater than 5 were recoded as 5 for disclosure concerns. A mean substitution was also performed for individuals who had missing data for this variable. If participants were lower than a value of 1, they were considered under the poverty threshold (69).

Diabetes Medication Use

NHANES uses the Lexicon Plus database which contains medication ingredients, medication classifications and medication uses. There are currently 11 classes of antidiabetic agents which can be prescribed for diabetes: alpha-glucosidase inhibitors, amylin analogs, antidiabetic combinations, biguanides, dpp-4-inhibitors, glp-1-agonists, insulin, meglitinides, sglt-2-inhibitors, sulfonylureas and thiazolidinediones. A total of 5 medication groups (Medgroups) were created grouped by body weight side effects. The no medication (NoMed) group consisted of individuals currently not on diabetes medications but still classified as a person living with diabetes. The weight loss medication (WlMed) group consisted of individuals taking diabetes medications associated with weight loss (10,36,38,70,71): biguanides, amylin analogs, glp-1-agonists, and sglt-2-inhibitors. The weight neutral medication (WnMed) group consisted of individuals taking diabetes medications that are not reported to have an effect on weight (10,72,73): alpha-glucosidase inhibitors, and dpp-4-inhibitors. The weight gain medication (WgMed) group consisted of individuals taking diabetes medication associated with weight gain (10,54,74,75): sulfonylureas, insulin, meglitinides or thiazolidinediones. Finally, the combination medication (CombMed) group consisted of individuals on more than one diabetes medication or taking antidiabetic combination medications.

Statistical Analysis

Descriptive characteristics were stratified by diabetes medication weight side effect groups. Data was shown as means (SE) or prevalence % (SE). MEC weighting variable was used for HbA1c, SBP, and DBP analyses while the fasting (SAF) weighting variable was used for analyses with fasting glucose, total cholesterol, HDL and triglyceride. Linear regression analysis was used to assess the association between HbA1c, SBP, DBP, fasting glucose, total cholesterol and HDL and triglycerides with BMI (continuous variable) and medication groups, with examination of main effects and interactions. With significant BMI-med group main effects and/or interactions, the regression was repeated with BMI was coded as nOB and OB (BMI cut-off 30 kg/m^2) to facilitated graphical representation and least squared means post hoc tests were used to determine obesity-medication group differences. All means were adjusted for sex, ethnicity, age, socioeconomic status, and smoking status. SBP and DBP analysis were further adjusted for high blood pressure medications. Total cholesterol, high density lipoproteins (HDL), and triglyceride analysis were further adjusted for lipid medications.

All analyses were performed using SAS version 9.4 and weighted to be nationally representative of the US population (SAS Institute Inc., Cary, NC, USA). Results were statistically significant if P <0.05.

3.4 Results

Descriptive Characteristics

Participant characteristics are shown in **Table 1.** The analysis consisted of 5 (medgroups) stratified based on body weight side effects: (NoMed n= 3161), (WlMed n=1453), (WnMed n= 47), (WgMed n= 756), and (CombMed n= 2536). Individuals in the NoMed group were on average younger (57.5 $\pm$ 0.4 years) than those in any other medgroup (58.4-68.0 years). The average fasting glucose in the CombMed group was the highest (9.2 $\pm$ 0.2 mmol/L) compared to all the other medgroups (7.3-8.1 mmol/L; P <.0001).

Association between BMI and Diabetic Medication use in Cardiovascular Health Risks

The weighted means for HbA1c, fasting glucose, SBP and DBP stratified by BMI group and medgroup are shown in **Figure 1**. Within the whole sample, there was no simple correlation between BMI and HbA1c (P=0.76). For HbA1c, the interaction effect between BMI and medgroup trended towards significance (P=0.08) with a significant main effect of medgroup (P < 0.0001). When stratified by medication group, there was a negative association between BMI and HbA1c in the WgMed group (P= 0.02), with no significant associations between BMI and HbA1c in the other medgroups. The HbA1c in the CombMed group (nOB: 7.9 $\pm$ 0.1%; OB: 7.7 $\pm$ 0.1%) was significantly greater than all medgroups for both BMI groups (nOB: 6.7-7.2%, OB: 6.7-7.0%, P < 0.05). Furthermore, within those with obesity, the HbA1c in the WlMed group was lower than all other medgroups (6.7 $\pm$ 0.1% versus 6.8- 7.7, P < 0.05).

Within the whole sample, there was no simple correlation between BMI and fasting glucose (P= 0.83). For fasting glucose, the interaction effect between BMI and medgroups trended towards significance (P=0.09) with a significant main effect of medgroup (P= 0.0023). When stratified by medication group, there was a significant positive association between BMI and fasting glucose in the NoMed group (P= 0.02) with no significant associations between BMI and fasting glucose in the other medgroups. Individuals in the CombMed group had significantly higher fasting glucose levels for a given BMI group (nOB: 9.2 $\pm$ 0.3 mmol/L; OB: 9.2 $\pm$ 0.2 mmol/L) compared to the NoMed, WlMed, and WgMed groups (nOB: 7.3- 8.3 mmol/L; OB: 7.8- 8.2 mmol/L; P < 0.05). The interaction effect between BMI and medgroup along with both main effects of BMI and medgroup were not significant for SBP and DBP (P > 0.05).

The weighted means for total cholesterol, HDL, and TG are shown in **Figure 2**. There was a simple negative correlation between BMI and total cholesterol within the whole sample (P= 0.04). For total cholesterol, the interaction effect between BMI and medgroups trended towards significance (P= 0.07), with a significant main effect of medgroup (P= 0.0061). When stratified by medication group and adjusted for demographic variables, socioeconomic status, smoking status and lipid medications, the association remained negative between BMI and total cholesterol in the NoMed, WlMed and WgMed groups ($P < 0.05$), but with no significant associations between BMI and total cholesterol in the WnMed or CombMed groups. Furthermore, total cholesterol in the NoMed group was significantly higher compared to the WlMed and CombMed group for both BMI groups ($P < 0.05$).

Within the whole sample, there was no simple correlation between BMI and TG ($P = 0.28$). For TG, the interaction effect between BMI and medgroup was significant ($P = 0.02$), with a significant main effect of medgroup ($P = 0.002$). When stratified by medication group and adjusted for demographic variables, socioeconomic status, smoking status and lipid medications, there was a positive association between BMI and TG in the CombMed group ($P = 0.002$), but with no significant associations between BMI and TG in the other medgroups**.** For HDL, there was a simple negative correlation for BMI ($P < 0.0001$), with no significant interaction effect between BMI and medgroup or main effect of medgroup ($P > 0.05$).

Table 1: Descriptive characteristics of US adults living with diabetes by medication class predicted weight effects (NHANES 1999- 2018)

Participant Characteristics	No Medication (n= 3161)	Weight Loss Medication (n=1453)	Weight Neutral Medication (n= 47)	Weight Gain Medication (n= 756)	Combination Medication (n= 2536)
Variable	**Mean (SE)/ Freq, SE**	**Mean (SE)/ Freq, SE**	**Mean (SE)/ Freq, SE**	**Mean (SE)/ Freq, SE**	**Mean (SE)/ Freq, SE**
Age (years)	57.5 (0.4)[cde]	58.4 (0.5)[cde]	68.0 (2.1)[abe]	65.2 (0.7)[abe]	60.6 (0.4)[abcd]
Sex (% female)	51.0, 0.1[b]	45.9, 0.1[ae]	49.9, 0.1	50.4, 0.1	53.8, 0.1[b]
Ethnicity (% white)	49.0, 0.1[bde]	56.2, 0.1[ad]	38.3, 0.1	38.0, 0.1[abe]	54.2, 0.1[ad]
Smoking Status (% smokers)	19.7, 0.1[bde]	13.1, 0.1[a]	10.4, 0.1	13.0, 0.1[a]	14.7, 0.1[a]
PIR (% below poverty)	16.2, 0.1[bd]	12.6, 0.1[a]	10.8, 0.1	11.9, 0.1[a]	14.8, 0.1
Body Weight (kg)	90.8 (0.6)[de]	93.1 (1.0)[d]	86.9 (3.6)[e]	88.5 (1.0)[abe]	95.1 (0.8)[acd]
Height (cm)	167.4 (0.3)[d]	166.6 (0.4)[e]	167.9 (2.8)	165.5 (0.5)[ae]	168.2 (0.3)[bd]
BMI (kg/m^2)	32.3 (0.2)[be]	33.4 (0.3)[ad]	31.1 (1.3)	32.2 (0.3)[be]	33.5 (0.2)[ad]
Waist Circumference (cm)	108.7 (0.4)[be]	111.1 (0.6)[ad]	107.5 (2.2)[e]	109.1 (0.7)[be]	112.7 (0.6)[acd]
Cardiovascular Health Risks					
Fasting Glucose (mmol/L)	7.8 (0.1)[e]	7.9 (0.1)[e]	7.3 (0.4)[e]	8.1 (0.2)[e]	9.2 (0.2)[abcd]
HbA1c (%)	6.8 (0.1)[e]	6.8 (0.1)[de]	7.3 (0.5)	7.0 (0.1)[be]	7.7 (0.1)[abd]
Systolic Blood Pressure (mmHg)	131 (1)[bd]	129 (1)[ade]	133 (4)	136 (1)[abe]	131 (1)[bd]
Diastolic Blood Pressure (mmHg)	72 (1)[cde]	71 (1)[cde]	66 (2)[ab]	69 (1)[ab]	68 (1)[ab]
Total Cholesterol (mmol/L)	5.2 (0.1)[bcde]	4.7 (0.1)[a]	4.5 (0.3)[a]	4.8 (0.1)[ae]	4.6 (0.1)[ad]
HDL (mmol/L)	1.3 (0.1)[e]	1.3 (0.1)[e]	1.3 (0.1)	1.3 (0.1)[e]	1.2 (0.1)[abd]
Triglyceride (mmol/L)	2.0 (0.1)[c]	1.9 (0.1)	1.5 (0.3)[a]	2.1 (0.2)	2.0 (0.1)

Weighted sample size: Medical Examination Centre = 298,416,774, Sample after fasting = 260,805,647, Waist Circumference (n) = 7555 Fasting Glucose (n) = 3936 SBP (n) = 7638 DBP (n) = 7592 Total Cholesterol (n) = 3885 HDL (n) = 3885 Triglyceride (n) = 3369

a = Significantly different compared to the no medications group ($P < 0.05$), b = Significantly different compared to the weight loss medication group ($P < 0.05$), c = Significantly different compared to the weight neutral medication group ($P < 0.05$), d = Significantly different compared to the weight gain medication group ($P < 0.05$), e = Significantly different compared to the combination medication group ($P < 0.05$)

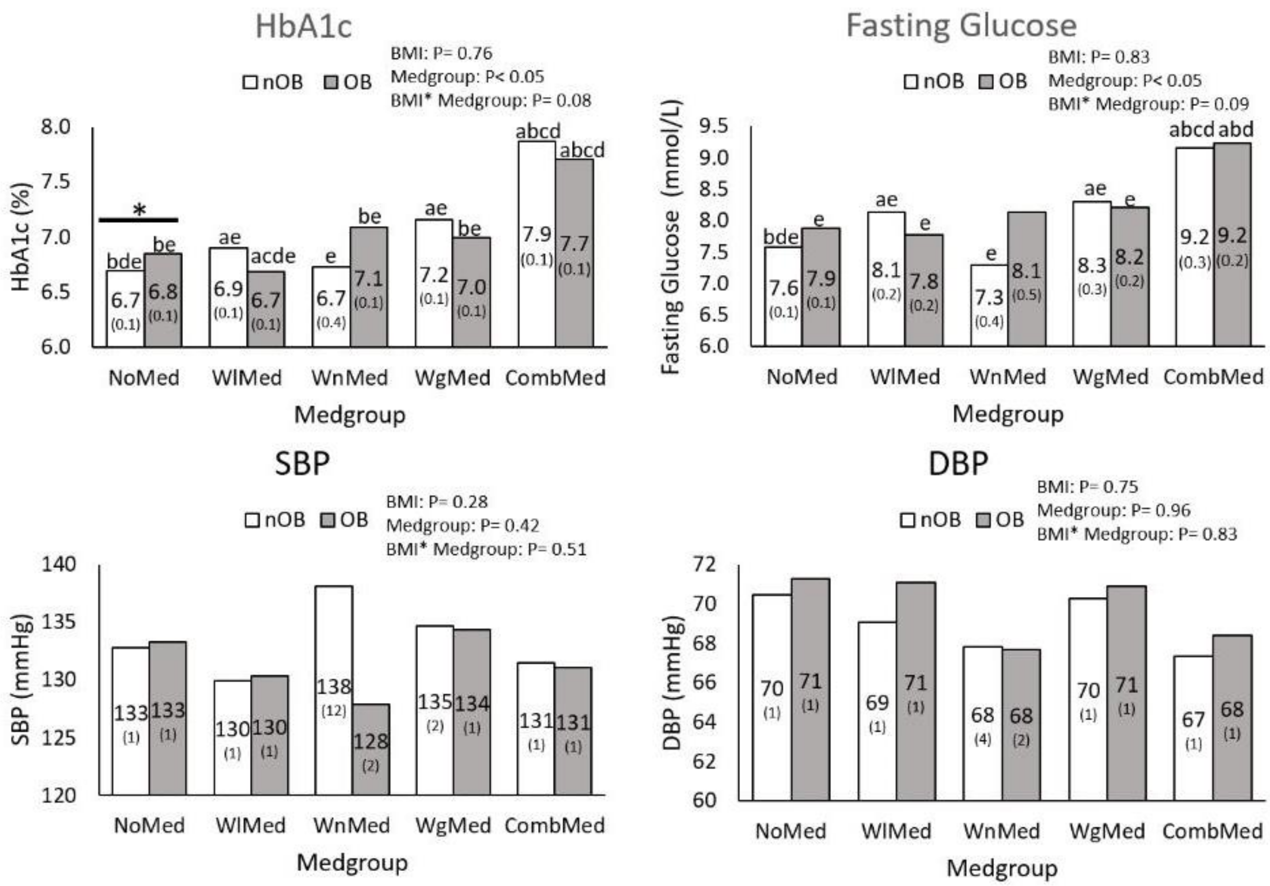

Figure 1: Weighted means for HbA1c: n = 7644, Fasting Glucose: n = 3631, SBP: n = 7359, and DBP n = 7295 by BMI and Medication Groups. Means are adjusted for sex, ethnicity, age, social economic status and smoking status. SBP and DBP are further adjusted for high BP medication status. Medgroup= medication group, nOB= BMI <30 (kg/m^2), OB= BMI >=30 (kg/m^2), BMI= body mass index, SBP= systolic blood pressure, DBP= diastolic blood pressure.
*= Significant BMI difference within medication group (P<0.05). a= Significantly different from NoMed group within BMI group, b= Significantly different from WlMed group within BMI group, c= Significantly different from WnMed group within BMI group, d= Significantly different from WgMed group within BMI group, e= Significantly different from CombMed group within BMI group.
NoMed= No Medications, WlMed= biguanides, amylin analogs, glp-1-agonists, and sglt-2-inhibitors, WnMed= alpha-glucosidase inhibitors, and dpp-4-inhibitors, WgMed= sulfonylureas, insulin, meglitinides or thiazolidinediones, CombMed= more than one medication and antidiabetic combination medications.

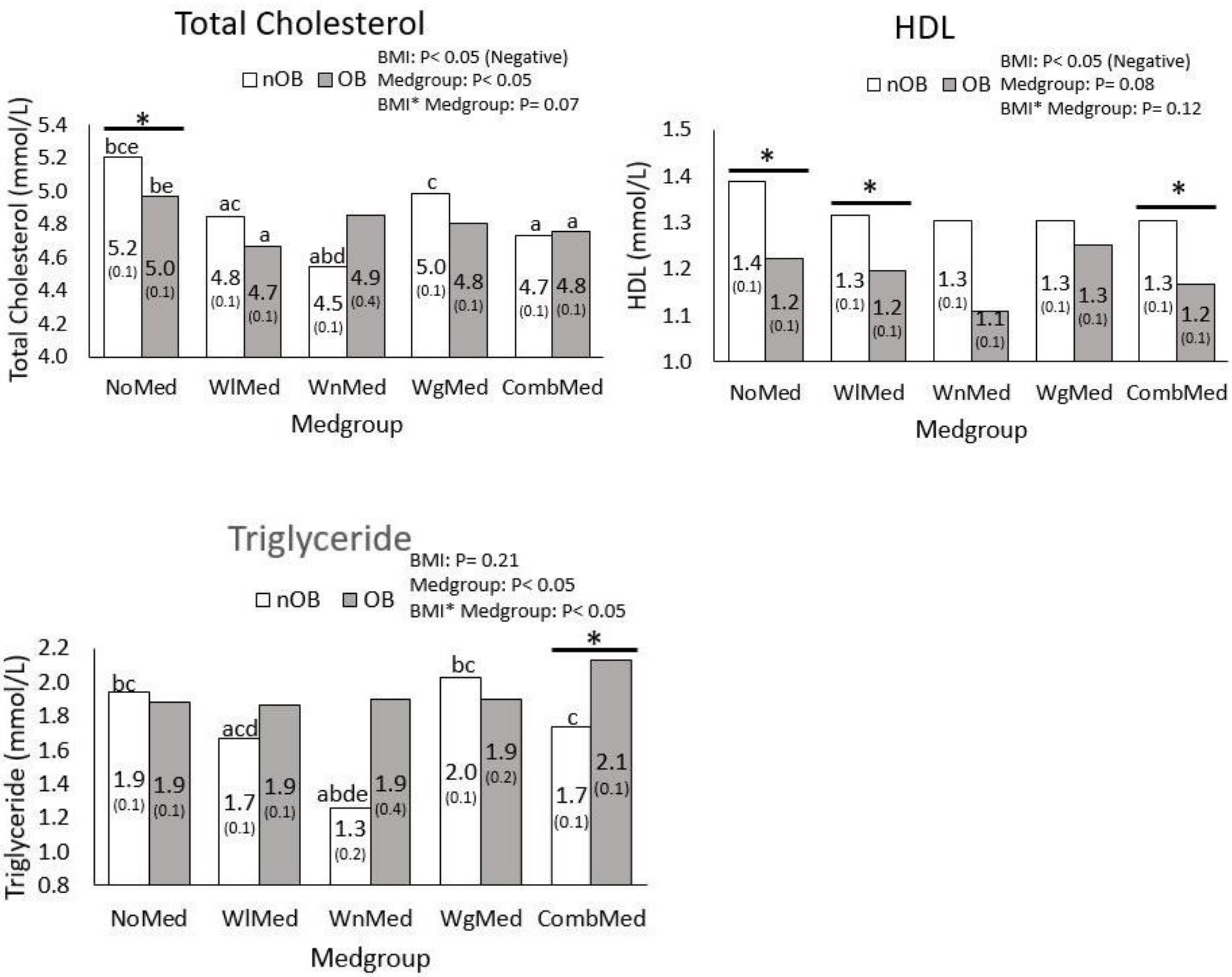

Figure 2: Weighted means for Total Cholesterol: n = 3579, HDL: n = 3579, and Triglyceride: n = 3111 by BMI and Medication Groups. Means are adjusted for sex, ethnicity, age, social economic status and smoking status and lipid medication status. Medgroup= medication group, nOB= BMI <30 (kg/m^2), OB= BMI >=30 (kg/m^2), BMI= body mass index, HDL= high density lipoproteins.

*= Significant BMI difference within medication group (P<0.05), a= Significantly different from NoMed group within BMI group, b= Significantly different from WlMed group within BMI group, c= Significantly different from WnMed group within BMI group, d= Significantly different from WgMed group within BMI group, e= Significantly different from CombMed group within BMI group.

NoMed= No Medications, WlMed= biguanides, amylin analogs, glp-1-agonists, and sglt-2-inhibitors, WnMed= alpha-glucosidase inhibitors, and dpp-4-inhibitors, WgMed= sulfonylureas, insulin, meglitinides or thiazolidinediones, CombMed= more than one medication and antidiabetic combination medications.

3.5 Discussion

Several medications used to treat hyperglycemia in T2D promote either weight loss or weight gain as a side effect of treatment. To our knowledge, the current study is the first to demonstrate that certain diabetes-related medications that lower glycemia but also impact body weight (increase or decrease) can potentially alter the commonly reported positive association between BMI with glycemic control and total cholesterol levels. Specifically, we found that those with T2D and obesity taking WlMeds were associated with lower HbA1c levels compared to those with T2D without obesity taking the same medication. As well, those with T2D and obesity taking WlMeds or WgMeds were associated with lower total cholesterol levels compared to those with T2D without obesity taking the same medications. Thus, diabetes medications may alter how obesity relates with cardiometabolic risk.

Excess body fat often leads to impaired whole body insulin sensitivity, beta-cell dysfunction and dysglycemia (14,76). Thus, those with a higher BMI are more likely to have T2D (77,78). T2D medications lower glucose levels by numerous mechanisms with some promoting clinically meaningful weight gain (i.e. insulin) while others promoting clinically meaningful weight loss (i.e., most oral hypoglycemic agents) (9). Thus, the known positive association between BMI and HbA1c may change when taking certain diabetes medications. Within the full sample of adults with T2D, there was no simple correlation between BMI and HbA1c observed in our study. In fact, those living with obesity and taking diabetes WlMeds had the lowest mean HbA1c (6.7 $\pm$ 0.1%) of all obesity-medication groups. Indeed, certain diabetes medications may improve glucose control and improve glucose utilization through various mechanisms that may or may not be independent of obesity. One of the effects of WlMeds such as amylin analogs, metformin and GLP-1-agonists is loss of appetite or feelings of satiety

(40,41,43). As such, individuals may lower HbA1c levels through reductions in obesity. Conversely, certain diabetes medications are reported to be associated with improvements in HbA1c despite concurrent weight gain (79,80). We observed a negative association between BMI and HbA1c for those taking diabetes WgMeds. The glucose lowering mechanism for diabetes WgMeds such as sulfonylureas, TZDs and meglitinides is increased insulin production (34,55,59). Greater insulin leads to lower blood glucose, greater energy storage, and weight gain as a consequence. Thus, while the association between BMI and HbA1c is often positive, this study demonstrates that diabetes medications that alter body weight may also alter and even invert the association between BMI and HbA1c.

It is commonly reported that individuals with obesity have higher total cholesterol levels compared to individuals without obesity (81,82). In contrast, we observe a simple negative association between BMI and total cholesterol in our population of adults with T2D. This negative association remained true for those taking NoMeds, WlMeds or WgMeds. Cholesterol synthesis is known to be positively associated with increased adipose tissues which stores cholesterol as triglyceride for later use (83,84). Many diabetes medications increase insulin production and sensitivity (10), which can increase the storage of triglycerides and lower total cholesterol. Thus, diabetes medications may be associated with improvements in total cholesterol despite increased BMI. We observed individuals taking WlMeds or CombMeds in our study had lower total cholesterol values than those on NoMeds for a given BMI. It is known that WlMeds, notably metformin may also reduce total cholesterol, specifically LDL cholesterol (85), potentially due to decreased appetite and reduced food intake (40,41,43). Together, these results suggest that certain factors such as T2D medications can significantly alter the often observed positive association between BMI and total cholesterol.

In this study, we demonstrate that the association between obesity and health risk in those taking diabetes medications may be altered. This may be expected given the several different mechanisms of action possible for diabetes medications. Although the association between obesity and health risk is well established (86,87), there are several other factors that are known to alter this association such as aging, physical activity and diet (88–90). Unlike past studies, BMI was not significantly associated with the majority of cardiovascular health risk factors examined in the current analyses. There are studies which suggest that the association between BMI and cardiovascular health risk is weaker in older individuals (91). In fact, some report inversed associations between BMI and mortality risk in older adults (92,93). These differences with aging, may have contributed to the unexpectedly weak association between obesity and health risk in this study as individual with T2D are generally older. Similarly, it is known that there are chronic and acute effects of physical activity which may obscure the association between BMI and CVH (94,95). Those living with T2D are advised at least 150 minutes a week of moderate to vigorous aerobic physical activity (96), but only 25% of individuals meet this guideline (97). Similarly, diet is known to have acute and chronic effects on cardiometabolic health risk (98,99). Although patients with T2D are prescribed a Mediterranean style diet (100,101), the adherence to this recommended dietary approach is low with less than 50% of individuals complying (102). Further, the association between dietary factors and health is complicated and often hard to capture with a single measure. Therefore, there are several factors along with diabetes medications that may influence the association between BMI and CVH.

There were strengths and limitations to this study. The use of NHANES allowed for easy access over a long period of time with a large sample size weighted to be nationally representative of the US population (66). Furthermore, the use of home interviews lowered the amount of nonresponse for demographic data and allowed for confounding adjustments in our analysis. The main limitation to this study was the use of cross sectional data which prevents the study from examining causal relationships. The sample size for individuals using WnMeds (n= 47) was small compared to other Medgroups thereby limiting our ability to observe significant group differences. Lastly, the duration or dosage in which individuals were taking specific diabetes medications was not assessed.

In conclusion, our study showed that those with T2D and obesity on WlMeds were associated with lower HbA1c levels compared to those with T2D without obesity on the same medication. Furthermore, those with T2D and obesity on WlMeds and WgMeds were associated with lower total cholesterol levels compared to those with T2D without obesity on the same medication. These findings imply the relationship between obesity status and cardiovascular health risks are complex and can change when taking diabetes medications. Further research should be conducted on those with T2D living with obesity have better long term health outcomes compared to those with T2D without obesity taking the same medication.

4.0 General Conclusion

Obesity is a rising health issue globally (1) which increases an individual's risk for developing further diseases, including T2D (3). The global prevalence of T2D is also on the rise with the number of individuals living with this disease predicted to climb over 366 million people by 2030 (103). As such, there is an increasing focus on T2D management, where lifestyle changes along with medications are crucial to reduce health outcomes.

Diabetes medications effectively reduce cardiovascular health risks such as fasting glucose and HbA1c (104), with various effects on body weight, such as weight loss or weight gain (10). There are several studies examining health changes for those living with T2D when taking diabetic medications (105,106). However, we further the literature by observing if these medications may be associated with differences in health risks between those living with and without obesity taking the same medication.

In conclusion, our study demonstrated that certain medications may be associated with greater control in HbA1c and total cholesterol levels for those living with obesity compared to without obesity when using the same medications. This suggests that in those using diabetes medications, the commonly observed positive associations between BMI and cardiovascular health risks may be altered. Further research should examine whether individuals with T2D living with obesity have better long term outcomes compared to those without obesity taking the same medication.

5.0 References

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