

The prevalence of Type 2 Diabetes among people living with HIV in Georgia

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Abstract

Background: The number of people living with human immunodeficiency virus (HIV) is increasing due to improved screening, faster diagnosis, newer methods, availability and acceptance of treatment, but the prevalence of non-communicable diseases, particularly metabolic disorders, has grown among HIV infected patients. The aim of the study was to calculate the prevalence of T2D among people living with HIV in Georgia and find the association between diabetes and other comorbidities to fill up knowledge gap.

Materials and methods: We have conducted a prospective cohort study among PLWH receiving care at the Infectious Diseases, AIDS and Clinical Immunology Research Center in Tbilisi, Georgia. The study included HIV positive adults (age ≥ 18 years) diagnosed in 2012-2018. Participants were followed-up from AIDS diagnosis till the 1st of October 2021. American Diabetes Association (ADA) guidelines were used to define hyperglycemia and diabetes.

Results : In total cohort 4.47% had prediabetes and 2.65% Type 2 diabetes. Our research demonstrates that the prevalence of hyperglycemia increases by the age. In total 171 (5.87%) participants had TB . Hyperglycemia and TB together was detected in 48.5% (83) of all TB patients. Relative risk (RR) of TB was 0.94 (95% CI : 0.85-1.56) . 32 participants had CKD, 50% (p=0.08) had hyperglycemia. CVD was detected in 92 participants, 44.6% (p=0.07) was hyperglycemic. 16 patients had a stroke, from which 11 (68.8%) had hyperglycemia. The RR of stroke =1.8 (95% CI : 1.45-4.76) . 550 (18.9%) patients had high total cholesterol and LDL level, 195 (35%) had hyperglycemia .

Conclusions: Prevention or early detection of T2D and timely management of metabolic disturbance, reduces risk of morbidity and mortality during HIV. Screening and management of hyperglycemia should be part of the routine HIV clinical services.

Keywords : *Type 2 diabetes, Hyperglycemia, HIV, Prevalence, Georgia*

Introduction

The number of people living with human immunodeficiency virus (HIV) is increasing due to improved screening, faster diagnosis, newer methods, availability and acceptance of treatment^{1,2}, but the prevalence of non-communicable diseases, particularly metabolic disorders, has grown among HIV infected patients^{1,3-6}.

A lot of studies have found that HIV infection and ART (antiretroviral treatment) are increasing insulin resistance, which leads Type 2 diabetes (T2D)⁷⁻¹⁰. Risk factors of T2D are well known in the general population, but HIV and ART are adding additional risk factors. Many factors influence the development of hyperglycemia and T2D during HIV infection, including the duration of the infection, systematic inflammation, the degree of immunosuppression, ARV (antiretroviral) medications, length of ART and coinfections⁷⁻¹⁵. Based on studies the prevalence of T2D ranges from 2% to 14%¹.

After ART has appeared the number of metabolic complications during HIV has increased^{6, 16-21}. The researchers thought, that metabolic complications were caused by nucleoside reverse transcriptase inhibitors (NRTI), because of mitochondrial toxicities. Other studies connected metabolic complications to protease inhibitors (PI). At the end researches suggested, that PIs and NRTIs have overlapping effect and they can induce insulin resistance (IR) and diabetes^{8, 12, 18}. Old age, weight gain, family history of diabetes are risk factors for development of diabetes during PI treatment¹¹.

Insulin resistance during PI treatment is increased via GLUT4 dependent^{8, 11} and independent mechanisms^{8, 12}. PIs interfere GLUT4 translocation from the cytosol of the cell to the cell's surface. Also, they alter adipogenic proteins and inhibit adipocyte differentiation⁸.

Pancreatic beta-cell lipotoxicity and lipodystrophy during ART, might be reason of glucose level elevation. Beta-cell function and insulin secretion is decreased by 25%–50% after PI treatment initiation⁸. When PIs are discontinued hyperglycemia resolves¹¹.

CVD (cardiovascular disease), CKD (chronic kidney disease) and metabolic disturbance have been linked to HIV and ARV medications^{5,6,10}.

In the general population The Framingham Risk Score (FRS) is a widely used tool to assess cardiovascular risk. It is used to estimate 10 years, CVD risk to the individual. Although its applicability to HIV patients is debatable. Unlike metabolic syndrome FRS is age dependent and takes in account cigarette smoking, LDL and total cholesterol concentrations. FRS divides individuals as low risk <10%, moderate risk 10-20% and high risk >20% of CVD^{22, 23}. FRS estimates that 1/3-1/4 of HIV infected adults are risk of CVD, but some authors are thinking, that it is underestimated²²⁻²⁴. Hyperglycemia is known to be a risk factor of CVD. Poor glycemic control is connected to microvascular and macrovascular disease²⁵. Stettler et al.

conducted a study in 2006 and showed, that the risk of macrovascular disease was significantly decreased by improving glycemic control²⁶.

The mechanism of vascular damage during hyperglycemia is unknown, but scientists support the idea, that it is caused by oxidative stress. Oxidative stress is the reason for micro and macrovascular complications during T2D²⁵. Gerich et al. suggest that inflammation, vasoconstriction and thrombosis are caused by oxidative stress and protein kinase C activation, which are induced by hyperglycemia²⁷.

One of the most frequent complication of HIV is a CKD. It ranges from 3.5 to 48.5%. HIV-associated nephropathy (HIVAN) is more common in young African adults, while HIV-immune complex disease (HIV-ICD) is more common in Europeans²⁸. On the other hand hyperglycemia and diabetes mellitus is a main cause of CKD, which leads to kidney failure. Studies have shown, that one third of CKD patients have diabetes, predominantly T2D²⁹.

Since 20th century, researchers have tried to find a link between T2D and Tuberculosis (TB). They were unable to distinguish whether T2D cause TB or vice versa. Some experts were discussing merging epidemics of TB and T2D³⁰. People with diabetes and hyperglycemia are more likely to develop TB, compared to non-diabetic cohort, due to increased susceptibility to infections³⁰⁻³³. They have 2.44 to 8.33 folds increased risk of TB compared to people without diabetes mellitus (DM)³². According to several studies, people with hyperglycemia are more prone to acquire multiresistant TB. The risk of complications, such as treatment failures and death are higher in people with diabetes mellitus. Furthermore, treatment of TB, might affect glycemic control negatively³⁰⁻³³.

Patients should be checked annually, because of higher prevalence of hyperglycemia and T2D during HIV. Prevention or early detection of T2D and timely management of metabolic disturbance, reduce risk of morbidity and mortality during HIV^{5, 7, 8, 17, 19, 34, 35}.

The prevalence of T2D in PLWH is unknown in Georgia. The aim of the study was to calculate the prevalence of T2D among people living with HIV in Georgia and find the association between diabetes and other comorbidities to fill up knowledge gap.

Material and methods

We have conducted a prospective cohort study among PLWH receiving care at the Infectious Diseases, AIDS and Clinical Immunology Research Center in Tbilisi, Georgia (IDACIRC). The study included HIV positive adults (age ≥ 18 years) diagnosed in 2012-2018 in IDACIRC. Every patient, who died or was lost within 6 months during follow-up were excluded from statistical analysis. Participants were followed-up from AIDS diagnosis till the 1st of October 2021. The total number of the study cohort was 2914.

The national AIDS health information system (AIDSHIS), a secure web-based database that collects data on all confirmed HIV cases, was used to retrieve all data, including demographic, clinical, and laboratory information.

National HIV guidelines recommended screening for glycemia at the beginning of HIV Diagnosis and then annually. American Diabetes Association (ADA) guidelines were used to define hyperglycemia and diabetes. In particular a fasting blood sugar level less than 100 mg/dl (5.6 mmol/L) is normal. A fasting blood sugar is considered as prediabetes if glucose level is from 100 to 125 mg/dl (5.6 to 6.9 mmol/L). If it's 126 mg/dl (7 mmol/L) or higher on two separate tests, patient has diabetes. A Postprandial blood sugar level less than 140 mg/dl (7.8 mmol/L) is normal. A reading between 140 and 199 mg/dl (7.8 mmol/L and 11.0 mmol/L) indicates prediabetes. Blood glucose more than 200 mg/dl (11.1 mmol/L) after two hours indicates diabetes³⁶.

Every single patient who had hyperglycemia even once was referred to endocrinologist for further diagnostics of diabetes. Participants were enrolled in the prospective study after giving an informed consent. Additional diagnostic tests, In particular, Oral glucose tolerance test (OGTT) with 75g glucose, glycated hemoglobin, HOMA Index, Lipid panel were conducted among the participants. We have estimated the prevalence of Diabetes, TB, CVD, CKD and stroke. The association between hyperglycemia and TB, CVD, CKD, stroke has been calculated.

For statistical analysis we have performed Descriptive and Bivariate analysis, using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

Ethical approval was obtained from the ethics committee of at Infectious Diseases, AIDS and Clinical Immunology Research center (N 20-006).

Results and Discussion

Our original sample consisted of 2914 HIV patients, the majority of the participants were male 2204 (75.6%). The majority of the patients represented age categories of 30-39 years old (31.3%) and 40-49 years old (29.7%). The median age was 52 (IQR=22-80). 11 (0.4%) Patients did not enroll in the study due to Covid-19 pandemic related situation. 7.4% of the participants were lost to follow up. For the period from 2012 to 2021 153 (5.2%) died. Hyperglycemia was detected in 381(13.1%) HIV patients. The detailed description of the sample characteristics is provided in the tables 1 and 2.

Table 1. Sample characteristics of people living with HIV (n=2914), Georgia, 2021

Variable	Total N (%)	Male	Female
Gender	2914 (100%)	2204 (75.6%)	710 (24.4%)
Hyperglycemia	381 (13.1 %)	326 (85.6 %)	55 (14.4 %)
Refused to participate for further examinations	11 (0.4 %)	9 (0.4%)	2 (0.3%)
Loss to follow up (2012-2021 years)	215 (7.4%)	183 (8.3%)	32 (4.5%)
Died during follow up (2012-2021 years)	153 (5.2%)	130 (5.9%)	22 (3.1%)
Performed diagnostic tests (OGTT Homa Index Lipid panel Glycated hemoglobin)	155 (5.3%)	145 (6.6%)	10 (1.4%)

Table 2. The prevalence of hyperglycemia by the age and gender among people living with HIV (n=2914), Georgia, 2021

Variable	Total N (%)	Normoglycemia	Hyperglycemia
Gender	2914 (100%)	2533 (86.9%)	381 (13.1 %)
Male	2204 (75.6%)	1878 (85.2%)	326 (14.8 %)
Female	710 (24.4%)	655 (92.25%)	55 (7.75 %)
Age (years)	2914 (100%)	2533 (86.9%)	381 (13.1 %)
19-29	501 (17.2 %)	496 (99.9%)	5 (0.1%)
30-39	913 (31.3%)	856 (94.7%)	48 (5.3%)
40-49	865 (29.7%)	753 (87.0%)	112 (13.0%)
50-64	577 (19.8%)	395(68.5%)	182 (31.5%)
>65	58 (2.0%)	24 (41.4%)	34 (58.6%)

The prevalence of hyperglycemia, was increasing with the age: 5 (1.31%) in the age group of 19-29 years, 48 (12.6%) in 30-39 years, 112 (29.4%) in 40-49 years, 182 (47.8%) in 50-64 years and 34 (8.9%) in older than 65 years (p value < 0.0001) (Table 3).

Table 3. The prevalence and distribution of hyperglycemia by age among people living with HIV (n=2914), Georgia, 2021

Prevalence of Hyperglycemia by age	Total sample (N=381) 13.1 %					P value	Median (IQR)
	19-29	30-39	40-49	50-64	>65		
	5 (1.31%)	48 (12.6%)	112 (29.4%)	182 (47.8%)	34 (8.9%)	<0.0001	52 (22- 80)

Additional tests (OGTT, Homa Index, Lipid panel, Glycated hemoglobin) have been conducted in 155 (5.3%) study participants. From 2914 HIV infected persons 4.47% (95% CI : 3.77 - 5.27) had metabolic syndrome and 2.65% (95% CI: 2.11 - 3.28) T2D. From 381 hyperglycemic participants 33.7% (29.0 – 38.5) had metabolic syndrome and 19.9% (16.0 – 24.3) T2D. From examined cohort (N=155) metabolic syndrome was detected in 82.2% (95% CI: 76.2 – 88.2) and T2D in 48.4 % (95% CI: 40.5 – 56.2) cases (Table 4).

Table 4. The prevalence of type 2 diabetes and metabolic syndrome among people living with HIV (n=2914), Georgia, 2021

Variable	Metabolic syndrome (N= 130)	95 % Confidence Interval (CI)	Type 2 diabetes (N= 65)	95 % Confidence Interval (CI)
Total (N = 2194)	4.47%	3.77 - 5.27	2.65%	2.11 - 3.28
Hyperglycemia (N= 381)	33.7%	29.0 – 38.5	19.9 %	16.0 – 24.3
Examined Cohort (N=155) (OGTT Homa Index Lipid panel Glycated hemoglobin)	82.2%	76.2 – 88.2	48.4 %	40.5 – 56.2

In total 171 (5.87%) participants had TB. Hyperglycemia and TB together was detected in 48.5% (83) of all TB patients. Relative risk (RR) of TB was 0.94 (95% CI: 0.85-1.56). 32 participants had CKD, 50% (p=0.08) had hyperglycemia. CVD was detected in 92 participants, 44.6% (p=0.07) was hyperglycemic. 16 patients had a stroke, from which 11 (68.8%) had hyperglycemia. The RR of stroke =1.8 (95% CI: 1.45-4.76). 550 (18.9%) patients had high total cholesterol and LDL level, 195 (35%) had hyperglycemia.

In our study the prevalence of hyperglycemia was significantly higher in male HIV infected participants, compared to the female HIV infected persons. Similar results have been reported from china (Shen et al. 2016)¹ in contrast to Spanish study (Alvaro-Meca et al. 2016). Spanish study outlined, that hyperglycemia was more prevalent in female HIV patients³⁷.

Our research demonstrates that the prevalence of hyperglycemia increases by the age. Results are not surprising, because, similar results have been reported in other studies about PLWH^{5, 15, 38, 39} and general population³⁶. Factors such as a family history of diabetes, weight gain, obesity and Insulin resistance can lead increased blood glucose levels¹¹. Furthermore, some antiretroviral drugs, such as PI's and NRTI's were related to the higher risk of T2D. Longer ART exposure was shown to be responsible for increased risk of hyperglycemia and diabetes mellitus^{1, 3, 4, 11}. In addition, there are a lot of discussions whether or not HIV infection alone can promote to the development of T2D. For example, a study of 2009-2012 years in China, conducted among newly diagnosed HIV patients who were not taking antiretroviral drugs, found a significant association between HIV and T2D, suggesting that hyperglycemia in HIV patients might be explained by not only ART use, but by HIV infection itself⁴⁰. Unfortunately, association between ART and diabetes or hyperglycemia could not be examined in our study as all the patients diagnosed with HIV in our cohort received ART immediately after the diagnosis.

Our study found out that the prevalence of T2D in total cohort was 2.65%. Similar results have been reported from Denmark (Rasmussen et al. 2012, Worm et al. 2009)^{41, 42} in contrast to researches in China and the USA, where prevalence of T2D was 9.7% and 10.3% respectively^{1, 5}. It should be taken into account that study cohort age was young (about 40 years old). T2D is more common in people above 40 years old, so theoretically it's possible, that young participants might decrease the prevalence of diabetes in the total cohort. Age distribution of hyperglycemia proved the same as it was the highest in people aged 40-65+. A similar association between increasing age and prevalence of T2D among PLWH found in many other studies^{5, 38, 39}.

Our study found that the prevalence of tuberculosis was 5.87% among people living with HIV. Based on our results the prevalence of TB with and without hyperglycemia did not differ significantly. Similar results have been found in UK by Pealing et al⁴³. Other studies revealed different results and showed, that diabetes and hyperglycemia were significantly associated with increased risk of TB^{30, 32, 33}. According to, the study in South Africa by Oni et al TB in hyperglycemic patients were 2.4 fold higher, compared to

normoglycemic cohort³³. Other studies suggested, that hyperglycemia is associated with higher mortality rates in TB patients^{19, 44, 45}.

In our research, the most common complication was dyslipidemia. We found out that 1/5 of our cohort had a high cholesterol level. As we mentioned HIV and ART are key factors in disease development^{8, 16, 23, 34, 46-48}. In addition, well know factors such as an unhealthy diet, low physical activity and cigarette smoking increase risk of dyslipidemia. If dyslipidemia is untreated, it leads to serious health complications and CVD.

CVD was detected in 92 participants, 44.6% had hyperglycemia. Based on RR normoglycemic and hyperglycemic cohort did not differ significantly. It might be explained by the fact, that our general cohort was young and the risk of CVD is increasing with the age. The Higher prevalence of CVD was reported in general population Georgia, compared to people living with HIV (15.3 vs 3.1 respectively).

Our study demonstrated that the risk of stroke was 2.2 times higher in hyperglycemic cohort, compared to people with normoglycemia. Similar results have been reported from another study By Michael D Hill in 2014⁴⁹. Nearly 30-40% of acute ischemic stroke patients have hyperglycemia. It has been reported, that hyperglycemia increases mortality rate significantly in patients with acute ischemic stroke⁵⁰.

In our research 32 participants had CDK and half of them had hyperglycemia. It is well known, that diabetes damages kidneys and causes diabetic nephropathy. Diabetic nephropathy is a major cause of CKD and renal failure^{29, 51}. Additional risk factors of CKD are HIV and ART by itself^{28, 29, 51, 52}. Based on our results the rate of CKD in hyperglycemic and normoglycemic cohort, did not differ significantly.

Hyperglycemia and other non communicable diseases should be monitored annually among people living with HIV to decrease morbidity and mortality rate. Prevention and early detection of noncommunicable diseases among PLWH will increase life expectancy and improve quality of life.

Conclusions

Noncommunicable diseases among PLWH, in particular hyperglycemia and T2D is a growing problem around the world. Our research addressed an issue. The prevalence of T2D and metabolic syndrome has never been calculated in Georgia before. We found out that the prevalence of T2D is 2.65% and is not higher, than prevalence in general population in Georgia. We think that further studies are needed to clarify an issue. Prevention or early detection of T2D and timely management of metabolic disturbance reduces risk of morbidity and mortality during HIV. Screening and management of hyperglycemia should be part of the routine HIV clinical services.

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ტიპი 2 შაქრიანი დიაბეტის გავრცელება აივ ინფიცირებულ პირებში, საქართველოში

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¹ინფექციური პათოლოგიის, შიდსისა და კლინიკური იმუნოლოგიის სამეცნიერო პრაქტიკული ცენტრი

აბსტრაქტი

შესავალი: ადამიანის იმუნოდეფიციტის ვირუსით (აივ) მცხოვრებთა რიცხვი იზრდება გაუმჯობესებული სკრინინგის, სწრაფი დიაგნოზის, ახალი მეთოდების, მკურნალობის ხელმისაწვდომობისა და მკურნალობის მიღების გამო. არაგადამდები დაავადებების, განსაკუთრებით მეტაბოლური დარღვევების გავრცელებამ მკვეთრად მოიმატა აივ ინფიცირებულ პაციენტებში.

კვლევის მიზანია ტიპი 2 შაქრიანი დიაბეტის გავრცელების გამოთვლა, შაქრიანი დიაბეტისა და თანმხლები დაავადებებს შორის ასოციაციის პოვნა, არსებული საკითხის ირგვლივ ცოდნის გაღრმავება.

კვლევის მეთოდები: ინფექციური პათოლოგიის, შიდსისა და კლინიკური იმუნოლოგიის სამეცნიერო პრაქტიკულ ცენტრში ჩავატარეთ პროსპექტული კოჰორტული კვლევა. კვლევაში მონაწილეობდა მოზრდილი (ასაკი \geq 18წელი) პირები, რომლებსაც აივ დიაგნოზი დაესვათ 2012-2018 წლებში. პაციენტზე დაკვირვება ხორციელდებოდა 2021 წლის 1 ოქტომბრამდე. ჰიპერგლიკემიისა და შაქრიანი დიაბეტის განმარტებებისთვის გამოვიყენეთ ამერიკის დიაბეტის ასოციაციის (ADA) გაიდლაინზი.

შედეგები: მთლიან კოჰორტაში 4.47% ჰქონდა პრედიაბეტი, ხოლო 2.65% ტიპი 2 შაქრიანი დიაბეტი. ჩვენი კვლევის მიხედვით ჰიპერგლიკემიის პრევალენტობა იზრდება ასაკის მატებასთან ერთად. ჯამში 171 (5.87%) მონაწილეს ჰქონდა ტუბერკულოზი. ტუბერკულოზის მქონე 48.5% (83) ჰქონდა ჰიპერგლიკემიაც. ტუბერკულოზის RR=0.94 (95% CI: 0.85-1.56). 32 მონაწილეს CKD ჰქონდა, მათგან 50% (p=0.08) ჰიპერგლიკემიაც. CVD 92 პაციენტს დაუფიქსირდა, მათგან 44.6% (p=0.07) კი ჰიპერგლიკემია ჰქონდა. 16 მონაწილეს ინსულტი განუვითარდა, მათგან 11 (68.8%) პარალელურად ჰიპერგლიკემიაც ჰქონდა. ინსულტის RR =1.8 (95% CI : 1.45-4.76) . 550 (18.9%) მონაწილეს მომატებული ჰქონდა საერთო ქოლესტერინისა და LDL კონცენტრაცია, მათგან 195 (35%) ჰიპერგლიკემიაც ჰქონდა.

დასკვნა: ტიპი 2 დიაბეტის პრევენცია, ადრეული გამოვლენა და მეტაბოლური დარღვევების დროული მართვა შეამცირებს ავადობისა და სიკვდილიანობის რისკს აივ ინფექციის დროს. ჰიპერგლიკემიის სკრინინგი და მენეჯმენტი ინტერგრირებული უნდა იყოს აივ-ის რუტინული კლინიკური კვლევის პაკეტში.

საკვანძო სიტყვები: ტიპი 2 შაქრიანი დიაბეტი, ჰიპერგლიკემია, აივ, პრევალენტობა, საქართველო