



# Problems of using Hydrochlorothiazide Diuretic in Adult Diabetic Patient in Diabetic Clinic of Adama Hospital Medical College, East Shoa Zone, Oromia Regional State, Ethiopia

Omer Aliyi, Mohammed Hussien\* and Belayneh Kefale

Department of Pharmacy, College of Medicine and Health Science, Ambo University, Ambo, Ethiopia

## Abstract

**Background:** Diabetes Mellitus (DM) is a group of common metabolic disorders that share the phenotype of hyperglycemia. Half century ago hydrochlorothiazide has been associated with a diagnosis of diabetes in hypertension treatment containing hydrochlorothiazide during long term therapy. This explained by association between glucose, potassium, and hydrochlorothiazide induced hyperglycemias and plasma insulin level. The objective of this study was to assess the problem associated with use of hydrochlorothiazide among adult diabetic patient in diabetic clinic of AHMC.

**Methodology:** A cross sectional study was carried out by reviewing patient information sheet and physician diagnosis card with a period from March, 25-May, 28, 2014. Data was collected from patient information sheet and physician diagnosis card by using check list and collected data was analyzing by using SPSS-20.

**Result:** In this study population the total of 1,200 patient cards with hypertension and type-2 diabetes were observed, from which only 60 patient have a problem associated with hydrochlorothiazide diuretic. Among these patient 55% were female and 38.3% were in the age group of 40-50 years and mean age was 51 years. Most of patient, 82% patient had increased FBS after HCT administration and around 90% of patient had decreased FBS after HCT discontinuation. Among the total number of the cases only in 5% showed high response to insulin and 37% low response to insulin. Most of the patient around 70% develop problem associated with HCT within start to six month.

**Conclusion:** In general in this study indicated that elevated fasting serum glucose level was the main problem associated with the use of HCT in adult diabetic patient.

**Keywords:** Hyperglycemia; High and low insulin response; Hypokalemia

**Abbreviations:** HCT : hydrochlorothiazide; DM : Diabetes Mellitus ; WHO : World Health Organisation; AHMC : Adama Hospital Medical College; ALLHAT: Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial; SHEP : Systolic Hypertension in the Elderly Program; IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose; FBS: Fasting Serum Blood Glucose Level

## Introduction

### Background Information

Diabetes Mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.

DM is classified on the basis of the pathogenic process that leads to hyperglycemias, as opposed to earlier criteria such as age of onset or type of therapy. The two broad categories of DM are designated type 1 and type 2. Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progress. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT) represents pre diabetic stage. In Ethiopia type 2 DM was more predominating than type 1 DM [1].

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 285 million in 2010. Based on current trend the International Diabetes Federation projects that 438 million individuals will have diabetes

by the year 2030. Accordingly there are about 12 million DM patient found in Africa and around 1.5 million found in Ethiopia in particular. Although the prevalence of both type 1 and type 2 DM increasing worldwide, the prevalence of type 2 DM is rising much more rapidly, presumably is because of increasing obesity, reduced activity levels as countries become more industrialized, and the aging of the population [1].

Thiazide diuretics have been available for the treatment of hypertension since the late 1950s, and reports of thiazide-associated hyperglycemia began appearing shortly thereafter. However, benzothiadiazine derivatives (hydrochlorothiazide most commonly) continue to be recommended as first-line therapy for hypertension without regard to metabolic status that resulted in diabetic's exacerbation [2]. Although there is not uniform agreement on the long-term significance of diuretic-induced diabetic, the controversy seems more about the relative benefits from improved BP control offset by the consequences of worsening metabolic status related to the thiazide diuretic. These patients are those likely to receive hydrochlorothiazide diuretics for decades, and the implications of

\*Corresponding author: Mohammed Hussien, Department of Pharmacy, College of Medicine and Health Science, Ambo University, Ambo, Ethiopia. Tel: +251913805290; E-mail: [gorawna@yahoo.com](mailto:gorawna@yahoo.com)

Received February 26, 2015; Accepted March 12, 2015; Published March 20, 2015

**Citation:** Aliyi O, Hussien M, Kefale B (2015) Problems of using Hydrochlorothiazide Diuretic in Adult Diabetic Patient in Diabetic Clinic of Adama Hospital Medical College, East Shoa Zone, Oromia Regional State, Ethiopia. Clin Pharmacol Biopharm 4: 134. doi:10.4172/2167-065X.1000134

**Copyright:** © 2015 Aliyi O, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

diuretic-induced diabetes may not be fully understood in those patients taking hydrochlorothiazide for relatively short-term period of time [3].

Metabolic effects of hydrochlorothiazide that can have a negative impact on diabetic risk profile include alterations in lipids, hypokalemia, impairment of glucose metabolism, and, therefore, the occurrence of type 2 diabetes by increasing hepatic insulin resistance. Early evidence emerged in the 1960s demonstrating aggravation of pre-existent type 2 diabetes mellitus in patients treated with hydrochlorothiazide diuretics. Since then, the adverse metabolic effects of hydrochlorothiazide diuretics have been demonstrated in a number of researches. There is also positive relation between thiazide-induced hypokalemia and the incidence of type 2 diabetes, most probably via the inhibitory effect of low potassium on insulin secretion [4,5].

Although hydrochlorothiazide and thiazide-like diuretics are indispensable drugs in the treatment of hypertension, their role as first-line or even second-line drugs is a provoking debate that doctors are faced with a difficult dilemma whenever they prescribe a HCT in diabetics, because of emergence of elevated FBS [4]. This also compromises the efforts of the health care system, policy makers and health care professionals in improving the health of the populations. In Ethiopia, particularly in the study area, little is known about the problem of HCT therapy in DM patients and associated factors. Therefore, the aim of this study will be to assess the problem and associated factors to hydrochlorothiazide therapy in adult diabetic patient visiting Adama Hospital Medical College.

### Statement of the problem

After introduction of hydrochlorothiazide in all over Ethiopia this diuretics associated with several potentially deleterious metabolic adverse effect and other complication attributed to problem of HCT therapy in diabetes. Among the major problem of HCT use in diabetics the frequently encountered one are diuretic induced hyperglycemia, hypokalemia and increased insulin resistance were the dominant ones [6]. Diuretics induced hyperglycemia can increase the risk of diabetic exacerbation which associated with a higher risk of all-cause mortality rate, for example, the incidence of coronary artery disease was 64% higher in the subjects who developed elevated FBS was the problem of HCT use in DM patient [3]. The risk of thiazide-induced diabetes is also dose dependent such that at 25 mg hydrochlorothiazide (HCT) there is substantial risk of impairing the glucose response. Since a high-dose HCT diuretic has a negative effect on glucose metabolism, it may be related to hypokalemia that can be corrected by potassium supplementation or combination of thiazide with ACE inhibitor or potassium-sparing agents might prevent thiazide-induced diabetes [7].

The other common problem of HCT Diuretics in diabetic adult patient may be hypokalemia that cause several other adverse reactions, potentially leading to discontinuation. Potassium is thought to play a key role in glucose homeostasis. Potassium is involved in the release of insulin as well as insulin-mediated glucose uptake into skeletal muscle. Both serum potassium depletion and glucose level elevation are common in patients treated with thiazide-type diuretics. Each 0.5 meq/L decrease in serum potassium during the 1st year of treatment was associated with a 45% higher adjusted diabetes risks that from decreased insulin secretion. Widespread use of low-dose thiazide can prevent this hypokalemia effect, but no information is available regarding the effects of low dose HCT diuretics on insulin action. Furthermore, hypokalemia can impair glucose metabolism by reducing insulin secretion and insulin sensitivity [6].

The other problem associated with HCT use in adult DM patient is increased resistance to insulin. The mechanism traditionally associated

with this increased risk of diuretic-associated diabetes mellitus was a reduction in serum potassium. Any medication that worsens insulin sensitivity, i.e., HCT diuretics will hasten the development of diabetes mellitus in those with impaired fasting glucose. However exact relationship between hypokalemia and worsening of insulin resistance is unclear but appears most pronounced in those with preexisting impaired glucose tolerance. There is evidence that prevention of hypokalemia with K<sup>+</sup> supplementation or potassium-sparing agents lessens the degree to which plasma glucose increased [8].

### Significance of the study

The results of this study contribute to increase the awareness of health care providers particularly physicians on the issue of prescribing HCT diuretic in adult diabetes patient and may aid them to develop strategies for improvement HCT diuretic induced hyperglycemia.

With increasing access to problem of HCT diuretic in adult diabetic patient in our country, there is an opportunity to better understand the benefit and limitation of HCT in DM clinic of AHMC. Data on the problem of HCT diuretic in adult diabetic patient in our country are scarce, so data can potentially provide good strategic approach in deciding problem of using HCT diuretic in adult diabetic patient in our country. It also provides important assistance to concerned organization especially for health institution.

This study also helps the different organization like government organization and Non-Government Organization [NGO] to use the result of the study in decision making related HCT in diabetic. The main aim of this study is to add to the existing body of knowledge about the problem associated with use of HCT in adult DM patient and lifestyle modifications necessary to maintain diabetes control, and to propose strategies that will assist policy makers and clinicians with diabetes management decisions.

### Objective of the Study

#### General objective

The general objective of this study was to assess the problems associated with use of hydrochlorothiazide among adult diabetic patient in diabetic clinic of AHMC.

#### Specific Objective

- To determine the number of patient who have developed a problem with using HCT in diabetes clinic of AHMC
- To describe the main problem associated with HCT in DM patient
- To identify type of the problem that resulted in dilemma of using HCT in DM patient.

### Methodology and Materials

#### Study area

Adama town is the capital city of Oromia regional state, Ethiopia and located 99 Km from Addis Ababa. There are different governmental and non-governmental institution in town such as 8 health Center, one referral hospital, one general hospital, 86 private clinics, and 75 pharmacies.

The study was conducted in Adama hospital medical college on adult patients who have diabetics' and hypertension cases whose patient's card contain hydrochlorothiazide. AHMC has 200 beds for inpatient with five disciplines (Surgery, Internal medicine, pediatrics, Gynecology/Obstetrics and ophthalmology) with four pharmacies

(OPD, ward, emergency and ART pharmacy). The hospital has about 465 workers of which 257 were health professionals. Adama hospital ranks second by patient intake next to Black lion hospital in Ethiopia.

### Study design and period

A cross sectional study on retrospective data was conducted by reviewing patient information sheet and physician diagnosis card from March, 25-May, 28, 2014.

### Population

**Source population:** The source populations for the study were all diabetic patients with hypertension that taking HCT during the follow up in DM clinic in of AHMC during previous one year from Sep. 2012 to May, 9, 2014.

### Sample size and sample technique

The study includes all DM patients with hypertension and type 2 DM who develop a problem with HCT use from 1200 patient with hypertension and type 2 DM, so that no sampling technique was used.

### Inclusion and exclusion criteria

The study includes all DM patients with hypertension who develop a problem with HCT use. The study exclude DM pediatric patient age group less than fifteen (15) years and DM patient who did not develop a problem with use of HCT.

### Study variable

#### Dependent variable

Fasting blood glucose level

Hypokalemia

Hyperglycemia

Insulin response

#### Independent variable

Age

Sex

Educational status

Marital status

Income

Residence

Religion

### Data collection

Data was collected from patient information sheet and physician diagnosis card by using check list.

### Data processing and analysis

After data have been collected it was categorized and analyzed by using SPSS-20.

### Ethical consideration

Before data collection to conduct this study ethical approval was obtained from Ambo University College of medicine and health science research team leader and the letter was submitted to Adama referral hospital medical director office prior to the beginning of undertaking the study in the area.

### Quality assurance

Before starting of the actual data collection pretest was done on 5% of patient information sheets to ensure their completeness, validity, reliability and consistency.

### Operational Definition

**Hyperglycemia:** Refers to blood glucose level >126 mg/dl.

**Hypokalemia:** refers to serum potassium concentration <3.5 meq/L.

**Diuretic:** are substance that remove fluides from the body by increasing urine out put.

**High response,** occur when FBS returned to normal with respect to insulin injection in diabetic patient using HCT.

**Low response,** reduction of FBS by 10 sin unit after insulin injection in diabetics' patient using HCT.

### Results

In this study a total of 1200 patient card with hypertension and type 2 diabetes were observed, from which only 60 patient a problem associated with hydrochlorothiazide diuretic had. Among these patient 55% were female and 38.3% were in the age group of 40-50 years and mean age was 51 years (Table 1).

In this study the dose of hydrochlorothiazide diuretic that were prescribed in all 60 patient with hypertension and type 2 diabetics was 25 mg daily, this dose was considered as high dose. During this study despite the necessity of lower dose, 12.5 mg per day of hydrochlorothiazide in diabetic patient none of the patient (100%) were found to take this advisable lower dose (12.5 mg).

Based on the data from the study the fasting plasma blood glucose level distribution of the patients since they start taking HCT was found with 5 patients (8.33% of the patient) reported of having fasting plasma blood sugar greater than 250 mg/dl followed by 16.6%, 40%, and 35% of the patient reported to have fasting plasma blood sugar in the range of 90-100 mg/dl, 100-150 mg/dl and 150-250 mg/dl respectively according to the following Figure 1.

Among 60 patient cards observed in DM clinic, around 49(82%) patient cards were showed to have more increased fasting plasma glucose level after long term use of HCT than at the start of HCT. Only 2% of the patients were reported to have unchanged fasting blood sugar after long term use of HCT (Table 2).

However, after discontinuation of HCT, from 60 patient cards nearly 54(90%) of the patient resulted in more decreased FBS than when on HCT (Table 3).

Response to insulin in the patient using HCT the response were reported as only 5(8.3%) patient were resulted in high response and 20(33%) were resulted in low response while the rest 35(58%) of the patient were not taking insulin. Based on sex from 5 high responding patients 3 of them were female and from 20 low responding patients 11 of them were female (Figure 2).

Time taken for HCT before it was resulted in increased FBS were reported as 70% of the patient were develop hyperglycemias within start to six month and 27% and 3% of the patient were develop hyperglycemias within 6 month-1 year and 1 year-2 year respectively. Regarding serum potassium electrolyte, in 100% of the study population no serum potassium electrolyte test was conducted in AHMC diabetic clinic.

Age(years)			sex	
	Frequency	Percent	Male	Female
18-30	--	--	--	--
30-40	8	13.3%	--	8
40-50	23	38.3%	8	15
50-60	16	26.7%	9	7
>60	13	21.75%	10	3
Total	60	100	27	33

Table 1: Age and sex distribution of study population in AHMC diabetes clinic, 2014.

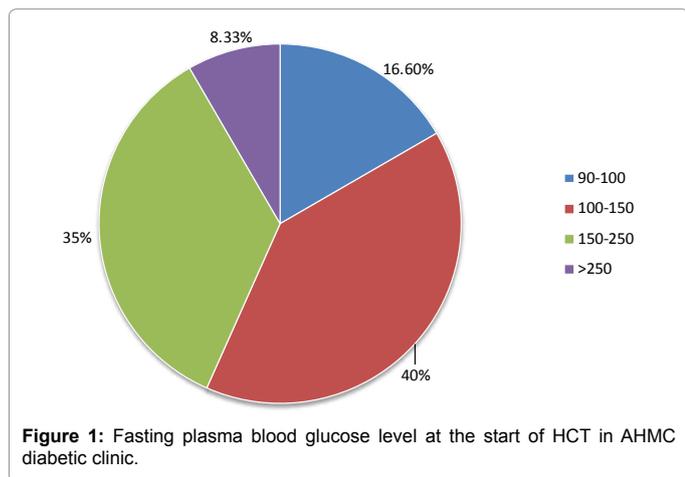


Figure 1: Fasting plasma blood glucose level at the start of HCT in AHMC diabetic clinic.

FBS after long use of HCT	Frequency	Percent
Increased	49	82%
Decreased	10	16.6%
Unchanged	1	2%

Table 2: Fasting plasma blood glucose level after long term use HCT in diabetic clinic of AHMC.

FBS after HCT discontinuation	Frequency	Percent
increased	3	5%
decreased	54	90%
unchanged	3	5%

Table 3: Fasting plasma blood glucose level after discontinuation of HCT in diabetic clinic of AHMC.

## Discussion

The primary goal of studying the use of HCT in adult diabetic patient was to reduce the adverse metabolic effect associated it, improving patient quality of life and reducing diabetic related mortality and morbidity through proper monitoring of laboratory value related to HCT such as serum electrolyte, glucose level and insulin sensitivity. If we are to continue to use HCT in adult diabetic patient we must minimize adverse metabolic effect and one way to do that is to use lower doses. This study was in line with study done in Belfast University of United Kingdom.

The most common problem that associated with the use of HCT in adult diabetic patient was an increase in FBS (82%), followed by low response to insulin injection (37%) which indicates insulin resistance that occurred as a result of hypokalemia caused by hydrochlorothiazide. This is consistent with study done in university of Atlanta on male and female of age group of 17-65 years [9].

After discontinuation of HCT use in adult diabetic patient in AHMC from targeted study population around 90% of patient found

to have decreased fasting serum blood glucose and only 5% of the patient found to have elevated serum blood glucose level after HCT discontinuation compared to 82% of the same study population with elevated serum blood glucose level before HCT discontinuation. Minor glucose elevation after HCT discontinuation may be due to non-adherence to medication and error in laboratory result while decreased serum blood glucose level after HCT discontinuation was indicating that HCT was highly associated with hyperglycemias. This study is similar with recommendation of current national clinical guide line.

From study population 55% were female and 38.3% were in the age group of 40-50 years which is the age group mostly associated with HCT induced serum blood glucose elevation because of this age group is among the older age group associated with elevated serum glucose. According to this study the patients in the older age are more associated with HCT induced hyperglycemias than patient in the younger age in AHMC (38% v 8.33%) and this is because of risk factor for hyperglycemias is higher at this age group. This study was in line with the study done in America were younger and older age prevalence of HCT induced hyperglycemias is 6.7% and 43% respectively.

Regarding response to insulin in the diabetic patient using HCT, only 5% of the patient reveals high response to insulin therapy while 37% of the study population shows low response to insulin during this study and this higher resistance to insulin therapy during HCT therapy is most probably due to hydrochlorothiazide induced hypokalemia as a result of decreased serum potassium level which cause decreased insulin secretion or decrease insulin sensitivity. This study was in line with study done in Texas, USA.

Regarding the dose of hydrochlorthiazide 25 mg dose per day was higher dose in diabetic patient that can be resulted in thiazide induced hyperglycemia in 82% of diabetic patient according to this study. This may be due to the greater serum potassium reduction with 25 mg of hydrochlorothiazide than 12.5 mg hydrochlorthiazide and Fasting serum insulin concentration was significantly increased after 12 weeks' treatment with Hydrochlorothiazide 25.0 mg but not with 12.5 mg. Endogenous glucose production was significantly higher after 25 mg compared with 12.5 mg HCT. This report was in line with the study done in Queen University of United Kingdom.

## Conclusion

In general, the result of this study indicated that elevated fasting serum glucose level was the main problem associated with the use of

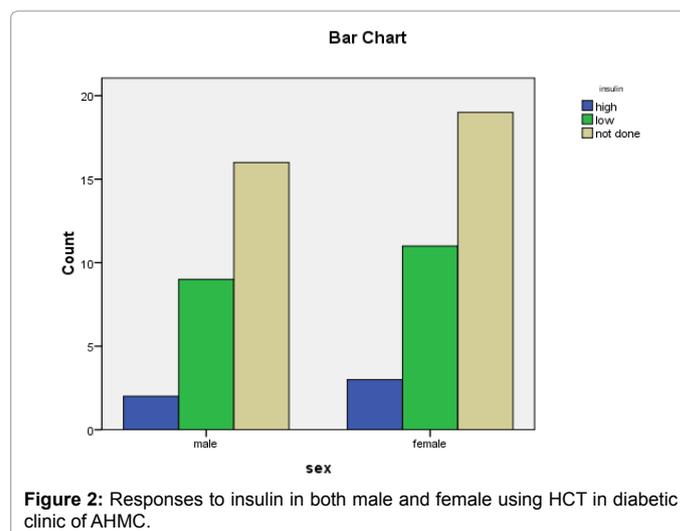


Figure 2: Responses to insulin in both male and female using HCT in diabetic clinic of AHMC.

HCT in adult diabetic patient among the study population. Decreased response to insulin and hypokalemia are the rest problem associated with HCT in adult diabetic patient. The dose of HCT above 12.5 mg per day was associated with HCT induced diabetic complications.

## Recommendation

Most problems associated with the use of HCT in adult diabetic patient require laboratory result for monitoring and follow up. Therefore, there should be enough qualitative and effective laboratory equipment and highly trained professional in Adama Hospital Medical College diabetic clinic.

- Before prescribing HCT in diabetic patient the value of serum electrolyte should be done.
- This health facility required to have electrolyte measuring device.
- There should be adequate potassium supplementation in patient with diabetics using HCT.
- There should be monthly glucose tolerance test in patient with diabetics using HCT.
- All physician should prescribe the lower dose 12.5 mg of HCT in adult diabetic patient in AHMC.

## Acknowledgements

We are very grateful to our college staff members for unreserved guidance and constructive suggestions and comments from the stage of proposal development to this end. We would like to thank Ambo University for supporting the budget which required for this research. Finally our deepest gratitude goes to Adama referral hospital staff workers who helped and allowed us in collecting and gathering data from the hospital.

**Funding:** Ambo University

**Conflict of interest:** None declared

**Ethical approval:** Approval and permission was sought from Ethical Review Board of College of Medicine and Health Sciences of Ambo University.

## References

1. Fuh MMT, Shieh SM, Wu DA, Chen YDI, Reaven GM (1987) Abnormality of carbohydrate and lipid metabolism in patients with hypertension. *Arch intern medicine*. 147:1035-1038.
2. Cutler JA, Barzilay JI, Davis BR (2006) Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: A report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 166:2191-2201.
3. Cutler JA (2006) Thiazide-associated glucose abnormalities: prognosis, etiology, and prevention: is potassium balance the key? *Hypertension* 48:198-200.
4. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL (2006) Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 48:219-224.
5. Verdecchia P, Reboldi G, Angeli F, Borgioni C, Gattobigio R et al. (2004) Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension* 43:963-969.
6. Stanley Feld (2002) American Association of Clinical Endocrinologists, American College of Endocrinology. Medical guidelines for the management of diabetes mellitus. *Endocr Pract* 8:40-82.
7. Savage PJ, Pressel SL, Curb JD, Schron EB, Applegate WB, et al. (1998) Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: The Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. *Arch Intern Med* 158: 741-751.
8. Samuelsson O, Hedner T, Berglund G, Persson B, Andersson OK (1994) Diabetes mellitus in treated hypertension: Incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial Goteborg, Sweden. *J Hum Hypertens* 8: 257-263.
9. Lundgren H, Bjorkman L, Keiding P, Lundmark S, Bengtsson C (1988) Diabetes in patients with hypertension receiving hydrochlorothiazide pharmacological treatment. *BMJ* 297:1512.