Post-Mortem Assessment of Glycemic Control in Sudden Diabetic Deaths Using Glycated Hemoglobin (HbA1c)

Saad kadhum Kareem

ABSTRACT:

BACKGROUND:

Post-mortem diagnosis of uncontrolled diabetes and its complications remains a common problem due to lack of unequivocal biochemical or histological proof of hyper or hypoglycaemia.In this study we evaluated glycated hemoglobin (HbA1c) as a post-mortem tool to identify uncontrolled diabetes.

OBJECTIVE:

To assess the use of glycated hemoglobin as an indicator for glycemic control in sudden diabetic deaths.

METHODS:

A cross-sectional study was carried out in the period from January 2015 to December 2015 on 47 sudden diabetic deaths and 22 natural non diabetic deaths at the Medico-Legal directorate in Baghdad. Information was collected from relatives, medical and police reports. A blood samples were drawn from the right ventricle of the heart of each decedent included in this study during autopsy. Blood was collected into sealed plastic tubes containing EDTA as anticoagulant and stored at 4°c temperature. These samples were analyzed within a period of 48 hours. One micro liter sample of thoroughly mixed whole blood was placed into the glass capillary tube provided in the HbA1c reagent kit and analyzed with variant-Hb- testing system. Data were recorded in the SPSS for window 11.0.

RESULTS:

The study showed that the mean age group of diabetic sudden death was 50.28+-10.01 while 44.36+-16.11 year was non diabetic sudden death.

Male gender was the predominant in both groups (diabetic and non diabetic) 27.30%, 21.30% respectively.

%HbA1c was significantly deferred in diabetic and non diabetic group, when it was positive 100% in diabetic group, while it's negative in non diabetic group (the cut off point is 6.5).

Type 2 diabetes was the predominant over type 1 with 59.60% and 40.40% respectively. The main system involved in sudden death in both study groups was the cardiovascular system accounting for 48.94% in diabetic group and 40.91% in control group, with the predominance of ischemic heart disease as the main cause of death in the system involved in both study groups accounting 40.43% for diabetic group and 22.73% for control group.

CONCLUSION:

HbA1c considered more reliable than post mortem glucose levels and provide guidance in the diagnosis of chronic diabetes mellitus in medico-legal autopsy cases.

KEY WORD: autopsy,diabetic death,HbAic

INTRODUCTION:

Diabetes mellitus (D.M) is a serious medical condition in which the metabolic use of glucose is impaired, resulting in chronic hyperglycemia. D.M. is one of the common causes of death due to a variety of complications [1].

Postmortem diagnosis of glucose metabolism disorders can be difficult and vague because of the lack of characteristic morphological findings .In many cases, the forensic pathologist may not be able to demonstrate unequivocal biochemical or histological proof for hyper or hypoglycemia [2]. Glycated hemoglobin (HbA1c) is a glycoprotein formed as a result of non-enzymatic addition of D-glucose to the hemoglobin B-chain. The amount of HbA1c in the blood is an indicator of long term glycemic control [3]. Terhi Keltanen , et al found that HbA1c analysis is a valuable tool alongside glucose and ketone bodies analysis in determining the metabolic state of deceased person in medico-legal autopsies [4].

Medico-Legal directorate, Baghdad.

AL-Kadhmya Teaching Hospital, Baghdad.

Post-mortem blood glucose estimation is not considered to be helpful, as it often might remain either normal or elevated in the early post-mortem period. This is due to the postmortem release of glucose from the body reserves, which render post mortem blood glucose level invalid in a diagnosis of diabetes mellitus [5,6]. On the other hand, Karlovsek MZ et al in their recent study concluded that combined glucose and lactate values may be elevated in cases of ante- mortem hyperglycemia, though not exclusively in cases of ante- mortem hyperglycemia, therefore it should not be used for diagnosing hyperglycemia [7]. Furthermore, they asserted that higher combined glucose and lactate values in the vitreous, though not diagnostic per se, should prompt pathologist to look for complementing postmortem HbA1C as most widely used measurement in evaluating long-term glycemic control as well as the risk for complications development and sudden death [7].

MATERIAL AND METHODS:

Selection of cases

A cross-sectional study was carried out in the period from January 2015 to December 2015 on 47 sudden diabetic deaths and 22 natural non diabetic deaths at the Medico-Legal directorate in Baghdad. All information and medical history were taken from medical files, relatives, police files and autopsy reports including (age, gender, and history of diabetes including (type, duration) and cause of death).

Collection of samples

Blood samples were drawn from (47) known sudden diabetic deaths and another samples from (22) non- diabetic natural deaths. Blood was collected into sealed plastic tubes containing the anticoagulant EDTA and stored at 4 degrees centigrade temperature. These samples of blood were collected at the time of autopsy from the right ventricle of the heart of included decedents autopsied in the Medico- Legal directorate in Baghdad.

Biochemical Analysis and Statistics

These samples were analyzed within a period of 48 hours. 1 micro liter sample of thoroughly mixed whole blood specimen's was placed into the glass capillary tube provided in the HbA1c Reagent kit and analyzed according to the manufacturers operating instructions with variant –Hb-Testing system (variant-B-thalasemia Haemoglobinopathy-1129, 1999). All samples were analyzed in the central laboratory of AL-Kadhmya teaching hospital in Baghdad. Data were recorded in the SPSS for windows 11.0

RESULTS:

The mean age value of diabetic cases was 50.28 ± 10.05 years (range 31-75 years with predominance of male gender 37 cases (78.70%) and type 2 D.M. account for 28 cases (59.60%) with main duration of diabetes was 11.9 ± 5.2 years (range 2-24 years) as shown in table 1 .

Table 1:The mean age values of the study groups according to some demographic factors.

		Study groups		P value
		Control	Diabetes mellitus	
Age (years)		44.36±16.11 (5-70)	50.28±10.05 (31-75)	0.128
Gender type	Female	6 (27.30%)	10 (21.30%)	0.397
	Male	16 (72.70%)	37 (78.70%)	
Duration of Diabetes mellitus		-	11.9±5.2 (2-24)	
Type of DM	Insulin dependent diabetes mellitus	-	19 (40.40)	
	Non insulin dependent diabetes mellitus	-	28 (59.60)	

The mean of %HbA1c in diabetic group was 10.94 $\pm$ 1.95 (range: 7.5-16.2%) as shown in table -2- .

Table 2: %HbA1C results for study groups.

		Study groups		P value
		Control	DM	
HbA1c ( )		5.26±0.53 (4.2-6.1)	10.94±1.95 7.5-16.2)	<0.001
HBA1C positivity	Positive	0 (0%)	47 (100%)	<0.001
	Negative	22 (100%)	0 (0%)	

The %HbA1c was above normoglycemic reference range for all cases within this population.
The most common cause of death in this group was related to the cardiovascular system as it was the most common system involved accounting for 23 cases (48.94%) within this system the most common cause was ischemic heart disease (19 cases) (40.43%) as shown in Figure-1- and table-3- respectively .
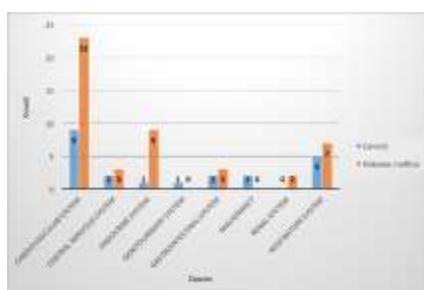

Figure 1:Demographic results of study groups (systemic causes of sudden death).

Table 3: Causes of sudden death of both study groups.

		Study groups	
		Control	Diabetes mellitus
Cardiovascular system	Congenital heart disease	1 (4.55%)	-
	Ischemic heart disease	5 (22.73%)	19 (40.43)
	Cardiac tamponade	-	1 (2.13)
	Cardiomyopathy	-	1 (2.13)
	Myocardial infarction	-	1 (2.13)
	Ruptured aortic aneurysm	-	1 (2.13)
	Myocarditis	2 (9.09)	-
Central nervous system	Epilepsy	1 (4.55)	-
	Post partum hemorrhage	1 (4.55)	-
	Cerebral hemorrhage	-	1 (2.13)
	Meningitis	-	1 (2.13)
	Ruptured berry aneurysm	1 (4.55)	
	Cerbrovascular accident	1 (4.55)	1 (2.13)
	Subarachnoid hemorrhage	-	1 (2.13)
Endocrine system	Acute hemorrhagic pancreatitis		1 (2.13)

	Diabetic ketoacidosis		3 (6.38)
	Hypoglycemia		2 (4.26)
	Pancreatitis		1 (2.13)
	Uncontrolled Diabetes mellitus		1 (2.13)
Gastrointestinal system	Liver cirrhosis	1 (4.55)	
	Liver disease	1 (4.55)	2 (4.26)
	Peritonitis		1 (2.13)
Respiratory system	Asthma	2 (9.09)	
	Pneumonia	3 (13.64)	5 (10.64)
	Tuberculosis		2 (4.26)
Genitourinary system	Maternal death	1 (4.55)	
Renal system	Renal failure		2 (4.26)
Malignancy	Brain tumor	1 (4.55)	
	Carcinoma of breast	1 (4.55)	
Total		22	47

Among non diabetic control group the mean age was 44.36± 16.11 years (range:5-7 years) with predominance of male gender 16 cases(72.70%) as shown in table -1- .The average of %HbA1c in non diabetic group was 5.26± 0.53% (range:4.2-61%) as shown in table-2-.

The %HbA1c for diabetic group was statistically significant different from non diabetic group at p<0.001 as shown in table -2-.

The most common system involved in the sudden death of non diabetic group was cardiovascular system 9 cases (40.91%) as shown in Figure -1-.

Among this system, the most common cause of death was ischemic heart disease 5 cases (22.73%) as shown in table -3- .

DISCUSSION:
It has been reported that D.M. increases the risk of mortality from cardiovascular diseases and in turn lead to a higher risk of sudden, unexpected death [8,9].Thus glycated hemoglobin must be measured in such group of natural deaths in order to characterized the glycemic control during the weeks preceding death and identify diabetes and its complications as the cause of death in autopsy cases of sudden death.

Comparative studies in decedents known to have D.M. versus controls have demonstrated that as HbA1c levels increase so does the frequency of D.M. and it's complications [10,11,12] .There is mounting evidence that type 2 D.M. is associated with an increased risk of mortality from coronary heart disease and sudden cardiac death [13,14] . In this study the incidence of sudden cardiac death increases markedly with age regardless of gender or race and this is in agreement with a study done by others [15, 16,]. Our study showed that women have a lower incidence of sudden cardiac death than men in both study groups which is the same fact showed by other epidemiological studies [15, 16]. This may be due, in part, to a lower overall burden of coronary heart disease in women with sudden cardiac death (SCD).

Among our diabetic group, type2 D.M. was the common type of diabetes mellitus,

Presented with sudden death. This might be related to the referral system in our health centers because many people with this type have no documents that they have D.M. due to poor compliance of such group with treatment and also relates to the fact that type 2 D.M. is associated with an increased risk of mortality from coronary heart diseases (CHD) and sudden death [4-13].

The range of %HbA1c for the controls group (non diabetic) was found to be 4.2-6.1 (mean 5.26± 0.53). This range is consistent with the reference range determined by our clinical laboratory for normoglycemic range which was below 6.5 considered to be normal. The %HbA1c for all decedents previously identified as diabetic exceed this range :(7.5-16.2) (mean 10.94± 1.95).

These results are consistent with histories that most of these individuals were in poor glycemic control and\ or that diabetes was contributing factor in their death. With respect to %HbA1c negative controls were found to differ statistically from the diabetic group at p<0.001. This study in agreement with winecker et al. reported that HbA1c levels is reliable indicator of post-mortem D.M. since this parameter showed glycemic control which appeared after weeks or few months before death and did not fluctuate greatly compared to glucose level in blood or vitreous humor[17] .So it is useful test in autopsy investigation of sudden death especially in those medico-legal cases with poor history of diabetes to clarify the presence or absence of diabetes and its complications. The increased risk of coronary heart disease mortality and sudden cardiac death among decedents with D.M, as in our study showed likely resulted , at least in part, from the increased presence and extent of coronary atherosclerosis (macro vascular disease) due to abnormalities of glucose\insulin homeostasis and\or other risk factors ,such as dyslipidemia , high blood pressure, and renal disease . D.M. also is associated with micro vascular disease and autonomic neuropathy; and , these non-coronary atherosclerotic pathophysiologic processes also have the potential to influence CHD mortalities and SCD among patients with diabetes [18,19] .This is in agreement with several numerous epidemiological studies have demonstrated association of diabetes with ischemic heart disease (IHD) among those without diabetes mellitus . [14 ,20,21] .Also from this study we emphasize that the determination of the HbA1c is also important for post-mortem diagnosis of fatal diabetic coma especially in young aged group presented with sudden death.

CONCLUSION:
1- HbA1c considered more reliable than post mortem glucose levels and provide guidance in the diagnosis of chronic diabetes mellitus in post-mortem investigations of sudden death.
2- This study highlights the usefulness of such biochemical test to identify diabetes mellitus and its complications as the cause of death in sudden diabetic deaths.

REFERENCES:
1. B.Zily,k.Alkass,S Bery,H.Druid.postmortem identification of hyperglycemia. Forensic science international, v: 185, issu 1-3 10 march 2009:89-95.
2. Gormsen H,Lund A. the diagnosic value of postmortem blood glucose determinations in cases of D.M. Forensic Sci Int 1985;28:103-7.
3. Khuu HM,Robinson CA ,Brissie RM, Konaard RJ. Postmortem diagnosis of unsuspected diabetes mellitus established by determination of decedent's hemoglobin A1C lens. J Forensic Sci 1999;44:643-46.
4. Terhi Keltanen, et al. Mzasum post.m. glycated hemoglobin-A comparison of three methods. Legal medicine;V 15,issu z, March 2013 :72-78.
5. Keltanen T,Sajantila A,Palo Ju,Partanen T, Valonen T, Lindroos K. Assessment of traub formula and ketone bodies in cause of death investigations.Int J Legal Med.2013; 127:1131-37.
6. Di Maio DJ,Di Maio VJ.Forensic Pathology,2nd edn,2001.New York:CRC Press;533-35.
7. Karlovsek MZ.Diagnostic values of combined glucose and lactate values in cerebrospinal fluid and vitreous humor-our experiences.Forensic Science International.2004;146S:19-23.
8. Kannel WB,Thomas HE jr.Sudden coronary death: the Framingham Study.Ann NY Acad Sci 1982;382:3-20.
9. Vinay Kumar,Abul K.Abbas,Jon C.Aster.Sudden cardiac death.Richard N.Mitchell.Robbins basic pathology.9th edition.Philadelphia: WB Saunders;2013:365.
10. Targher G,Bertolini L, Zenari, Lippi G, Zoppini G, et al.Diabetic retinopathy is associated with an increased incidence of cardiovascular events in type 2 patients. Diabet Med.2008;25:45-50.
11. Wheeler SG, Ahroni JH, Boyko EJ. Prospective study of autonomic neuropathy as a predictor of mortality in patients with diabetes. Diabetes Res Clin Pract. 2002;58:131-38.
12. Suarez GA, Clark VM, Norell JE, Kottke TE, Callahan MJ, Obrien PC, et al. Sudden cardiac death in diabetes in 54 young adults: a30 year population-based study . Am J Cardiol.1995;76:148 -52.
13. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB , D Agostino RB,Sr, et al . Trends in cardiovascular complications of diabetes.JAMA.2004;292:2495-99.

14. Jouven X, Lemaitre RN, Rea TD, Sotoodehnia N, Empana JP, Siscovick DS. Diabetes,glucose level,and risk of sudden cardiac death.Eur Heart J. 2005;26:2142-47.

15. Albert CM, Chae CU,Grodstein F,Rose LM,Rexrode KM, Ruskin JN, Stampfer MJ, Manson JE.Prospective study of sudden cardiac death among women in the United States.Circulation.2003;107:2096-101.

16. Krahn AD, Connolly SJ, Roberts RS, Gent M.Diminishing proportional risk of sudden death with advancing age:implications for prevention of sudden death. Am Heart J.2004; 147:837-40.

17. Winecker RE, Hammet-Stabler CA, Chapman JF, Ropero-Miller JD.HbA1c as a postmortem Tool to Identify Glycemic control. J Forensic Sci, 2002; 47:395-476.

18. Targher G,Bertolini L,Zenari L,Lippi G,Pichiri I,Zoppini G,et al.Diabetic retinopathy is associated with an increased incidence of cardiovascular events in type 2 diabetic patients.Diabet Med.2008;25:45-50.

19. Ewing D,Campbell I,Clarke B. The natural history of diabetic autonomic neuropathy. Q J Med.1980; 49:95-108.

20. Kucharska-Newton AM,Couper DJ,Pankow JS,Prineas RJ, Rea TD,Sotoodehnia N,et al. Diabetes and the risk of sudden cardiac death, the Atherosclerosis Risk in Communities study .Acta Diabetol.2009. PMC free article.

21. Pankow JS,Kwan DK,Duncan BB,Schmidt MI,Couper DJ,Golden S,et al.Cardiometabolic risk in impaired fasting glucose and impaired glucose tolerance: the Atherosclerotic Risk in Communities Study. Diabetes Care.2007; 30:325-31.