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Relationship Between Age and Diabetic Treatment Type on the Frequency of Hyperglycemic Episodes Monitored by Continuous Glucose Monitoring

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1. Introduction

Diabetes mellitus is a chronic debilitating disease affecting over 23 million children and adults in the United States. Many of the ill effects of this disease lie in part with uncontrolled glucose levels in the body. Hypoglycemia increases the risk of cardiovascular and cerebrovascular events, progression of dementia, injurious falls, emergency department visits, and hospitalizations (Desouza, 2003; Leese, 2003; Schwartz, 2008; Whitmer, 2009).

Hypoglycemia-associated autonomic failure is another major complication that diabetic individuals go through when their glucose levels are not properly regulated. In this complication, antecedent hypoglycemia causes both defective glucose counter-regulation and hypoglycemia unawareness (by reducing autonomic and neurogenic symptom response) thus making it difficult for patients to properly sense a hypoglycemic event and thus cause further complications in the future (Cranston, 1994; Cryer, 2004; Dagogo-Jack, 1994, Fanelli, 1994).

Hyperglycemia is associated with secondary damage to many organ systems especially the kidneys, eyes, nerves and blood vessels. Hyperglycemia is associated with both macro- and microvascular complications. The macrovascular complications include increased risk of myocardial infarction as well as stroke, cerebrovascular disease, and coronary artery disease (Kannel, 1979; Lehto et al., 1996). On the microvascular level, hyperglycemia is associated with vascular damage, leakage, and edema. Such inflammation can lead to occlusion and ischemia as well as nerve damage (Kannel, 1979).

Since the Diabetes Complications and Control Trial (DCCT) established hemoglobin A1C as the gold standard of glycemic control there has been a lot of research on other factors that might better predict the risk of diabetic complications. One such factor has been glycemic variability. Large changes in glycemic levels lead to production of reactive oxygen species (ROS), which in turn accelerate the micro- and macrovascular complications of diabetes. It is

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also possible that neglecting these variations in glycemic control could lead to misinterpretation of the risk of diabetic complications even if the mean A1C levels fall within the normal accepted range (Hirsch & Brownlee, 2005).
However, for a variety of reasons ranging from biomedical to psychosocial it is difficult to achieve optimal glycemic control (Amir et al., 1990). Continuous glucose monitoring (CGM) provides a useful method to help monitor glucose values and to provide useful feedback to more effectively control glycemic levels (Klonoff, 2005). In a multicenter clinical trial studying two groups, one using CGM and the other using self-glucose monitoring it was found that there was a significant improvement in hemoglobin A1C in patients using CGM as compared to patients using self-monitored finger stick glucose measurements after a 26 week trial (Tamborlane et al., 2008).
To further study some of these observations, in our study we used CGM over a 72 hour period to examine 84 male patients who had been diagnosed with either Type I or II diabetes. Our goal was to characterize the time the patient spent in a hypo-, hyper-, and eu-glycemic state with respect to age and the treatment type the patient received (oral medication vs. insulin).

2. Methods

Eighty-four treated adult male diabetic patients (18 oral treatment, 51 insulin only, and 15 both oral and insulin) were studied. All patients had attended a comprehensive diabetes clinic on a regular basis and had received diabetes education including diet, exercise and self-monitoring of blood glucose (SMBG) instructions.
Assessment of clinical data included age, sex distribution, and duration of diabetes, body mass index, diabetic complication (i.e. Diabetic neuropathy, retinopathy, nephropathy, cardiovascular disease and peripheral vascular disease). Pertinent laboratory data included HbAlC, plasma glucose, creatinine, liver function tests, lipid levels and microalbuminuria. The patient's home medications were also reviewed for potential effect on glucose homeostasis.
A CGMS sensor was inserted and calibrated according to the Minimed Medtronic procedure. Patients were instructed to continue with their regular lifestyle, to keep a food diary and to record event markers into the monitor e.g. insulin administration, exercise, SMBG and hypoglycemic episode. After 72 hours, the monitor was removed and the data were downloaded using Minimed Solutions Software version 2.0b.

2.1 Statistical analyses

Standard procedures were used to calculate the means, SD, SEM, hyperglycemia frequency and correlation coefficients. SMBG glucose values were paired with corresponding CGMS glucose values for linear regression analyses. Blood glucose concentration >140 mg/dL for at least 30 minutes indicated hyperglycemia. Hyperglycemic prevalence was calculated as the percentage of a specified time period spent during hyperglycemia. Changes in blood glucose > 100mg/dL within a 60-min period were defined as rapid glucose excursions.

3. Results

During the 3-day evaluation, 84 men provided a continuous measure of blood glucose levels using a CGM device[4]. The participants mean age was = 66.17 (± 11.36) years, with N=36

subjects younger than 65 and N= 48 subjects 65 and older. Of the 84 patients, 18 were on oral medications alone, 51 were on insulin alone, while 15 were on both. Table 1 provides demographic information including age, BMI, systolic blood pressure and HbA1C. The correlations among BMI, systolic BP, hemoglobin A1C and age are presented in Table 2. The analysis of the glycemic levels were divided into 3 time periods: 6 am – 6 pm (daytime), 6 pm – midnight (evening), and midnight – 6 am (early morning).

Age	$\bar{x}$ = 66.17 ± 11.36
BMI	$\bar{x}$ = 30.3 ± 5.86
Systolic Blood Pressure	$\bar{x}$ = 135.04 ± 18.9
HbA1C	$\bar{x}$ = 7.76 ± 1.62

Table 1. Demographics (N = 84)

	Age	**BMI**	**HbA1c**	**Systolic BP**
Age	1	-0.15	-0.41*	0.32*
BMI	-0.15	1	-0.11	-0.06
HbA1c	-0.41*	-0.11	1	-0.15
Systolic BP	0.32*	-0.06	-0.15	1

*p <.05; **p < .01

Table 2. Zero order correlations

Overall, a greater percentage of time was spent in hyperglycemia during the day (57.86% ± 14.59) than at night (16.11% ± 10.40), $t_{(83)} = 16.50$, $p < 0.01$. The analysis of hypoglycemic and euglycemic states showed no statistically significant difference (multiple regression analysis) between time intervals when comparing the association with age, BMI, treatment, HbA1c, or any other predictive variables. Also no significant findings were seen in the evening hours (6 pm to midnight) when examining the same variables for either age or treatment type for any glycemic state.

The effects of Age Grouping (<65 and ≥65) on the percentage time that subjects were in the hyperglycemic state during the early morning was evaluated with multiple regression analyses using covariates (BMI, systolic blood pressure, and hemoglobin A1C) that were found to be statistically significantly related to hyperglycemic events. The model outlined in Table 3 included BMI entered on the first step, systolic blood pressure entered on the second step and HemoglobinA1c (HbA1C) entered on the third step. The same analysis was done for the daytime interval. Increasing values of HbA1C were associated with a significantly greater percentage of time in the hyperglycemic state, as expected, but only during the early morning hours.

However, BMI and systolic blood pressure were not significant predictors of percentage time in the hyperglycemic state. On the other hand, subjects older than 65 years exhibited a significantly greater percentage of time in the hyperglycemic state for the daytime interval and a lower percentage of time in the hyperglycemic state for the early morning interval. The opposite pattern was found for subjects younger than 65. That is subjects younger than 65 spent a greater percentage of time in hyperglycemia during the early morning interval

and a lower percentage of time in hyperglycemia during the daytime interval. The difference between the age groups for the percent time hyperglycemic during the day was significant, p = 0.02 while a borderline difference was evident during the early morning, p = 0.06. These effects are displayed in Figure 1 and Table 3. In addition, Figure 2 displays the percentage of time in the hyperglycemic state as a function of age for the early morning period (A) and for the daytime (B). The distinctive positive and negative effects of increasing age has a beneficial effect (lower percentage time in hyperglycemia) during early morning and a detrimental effect (higher percentage time in hyperglycemia) during the day. Although these effects were not significant, the results are of interest due to the fact that clinical evidence of hyperglycemic patterns can help physicians better control glycemic excursions. The reasoning behind this finding remains unexplained.

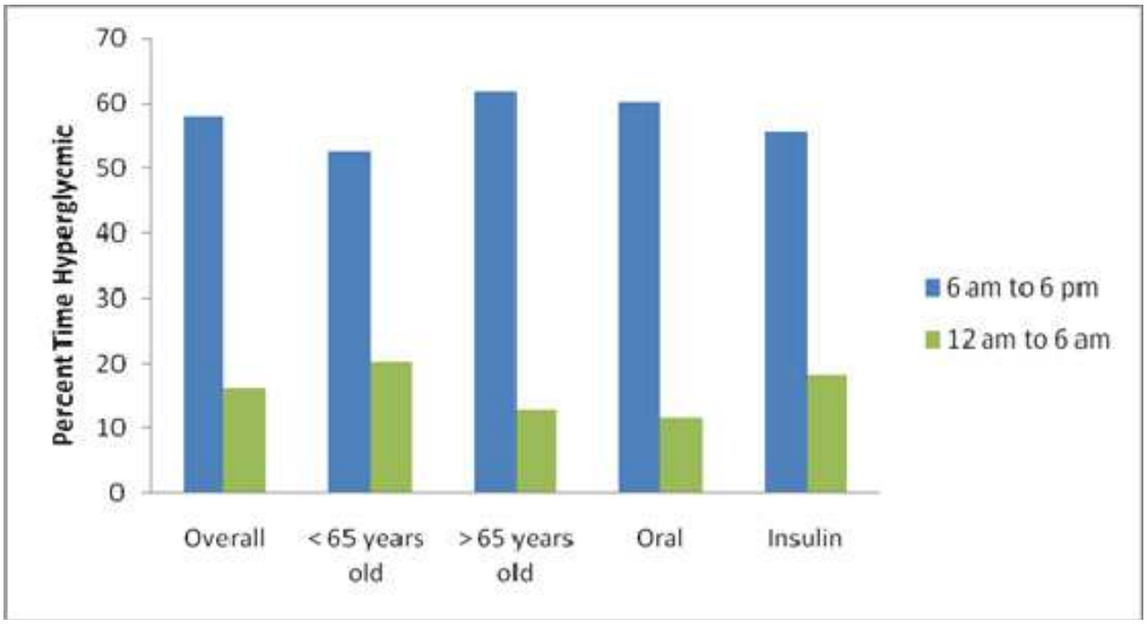

Fig. 1. Percent Time Hyperglycemic based on Age and Type of Medication (Oral, Insulin)

	% Time Hyperglycemic from 12 am to 6 am		% Time Hyperglycemic from 6 am to 6 pm	
Predictors	**Beta**	**R^2**	**Beta**	**R^2**
BMI	0.68	0.01	- 0.09	0.01
Systolic Blood Pressure	-0.15	0.02	0.05	0.00
Hemoglobin A1c	0.31	0.09*	- 0.16	0.03
Age Group	0.24	0.04 ‡	- 0.30	0.07**

Beta = Standardized Beta
*p<.05; **p< .01; ‡p < 0.06

Table 3. Multiple Linear Regressions – Relationship between Age Group and % Time Hyperglycemic

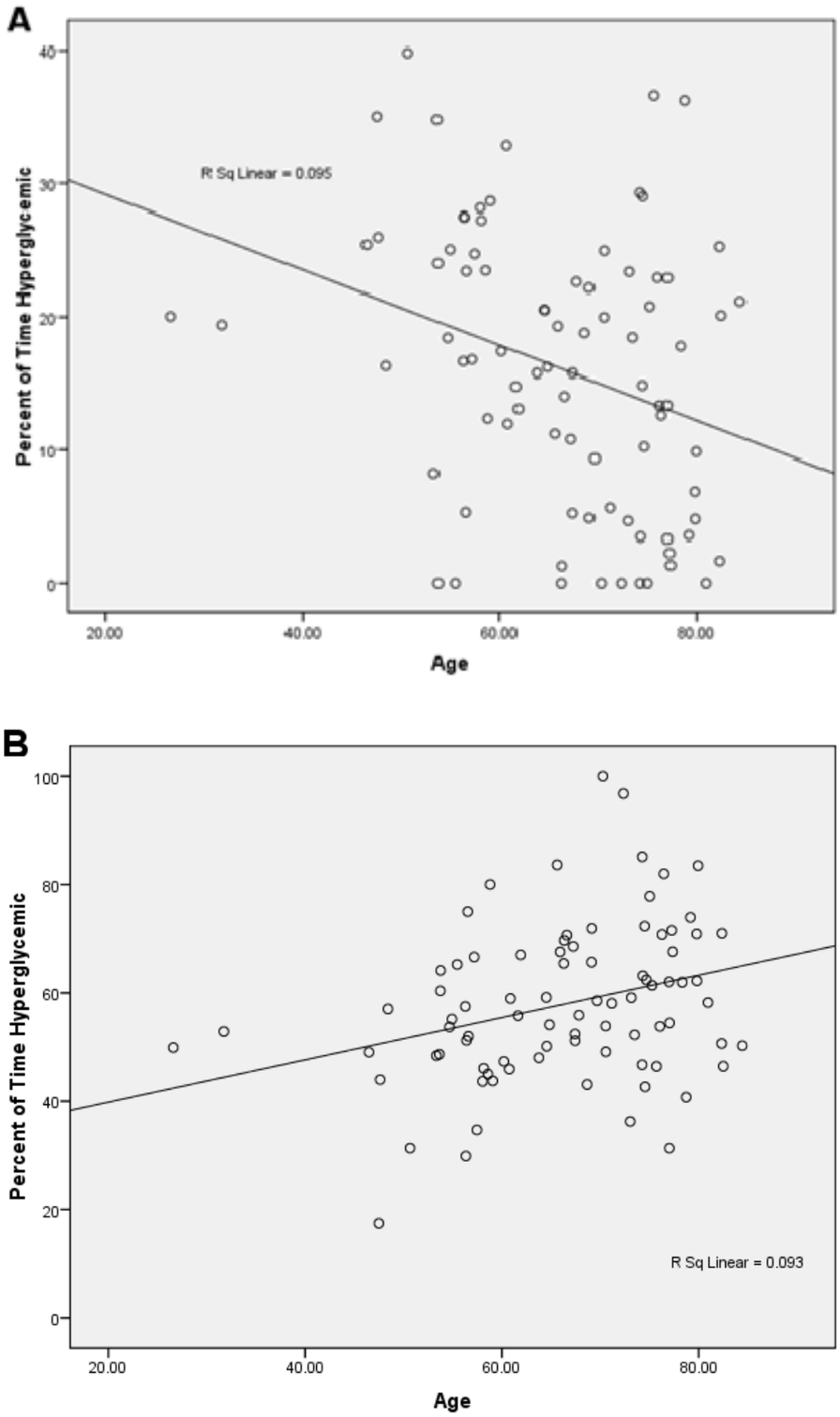

Fig. 2. Percentage of time spent in hyperglycemia as a function of age during the time interval from 12 am to 6 am (A) and from 6 am to 6 pm (B)

Multiple linear regressions (Table 4) examine the effects of diabetes treatment type on the percentage of time that subjects were in the hyperglycemic state. The groups were analyzed based on treatment modality (oral, insulin, or both). To further clarify the analyses only those receiving *either* insulin or oral medication were examined. The results indicated that during the early morning period, those taking oral medication exclusively exhibited a lower percentage of time in the hyperglycemic state (p = < 0.06). These effects are displayed in Figure 3. Similar findings were not found in the other two time periods.

	% Time Hyperglycemic from 12 am to 6 am		% Time Hyperglycemic from 6 am to 6 pm	
Predictors	**Beta**	**R^2**	**Beta**	**R^2**
BMI	-0.02	0.00	- 0.11	0.01
Systolic Blood Pressure	-0.24	0.06*	0.24	0.06*
Hemoglobin A1c	0.28	0.07*	- 0.12	0.01
Type of Medication	0.22	0.05‡	-0.13	0.02

Beta = Standardized Beta; Medication Type: Oral= 1, Insulin = 2
* p< .05; **p< .01; ‡p < 0.06

Table 4. Multiple Linear Regressions – Relationship between Medication Type (Oral, Insulin) and % Time Hyperglycemic

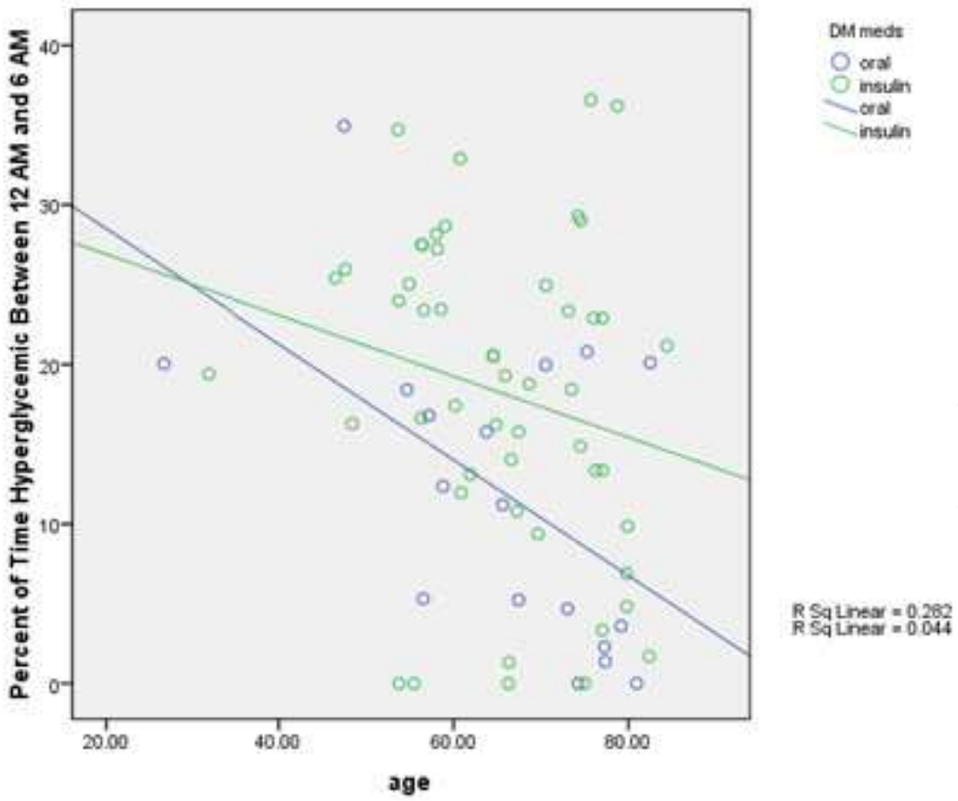

Fig. 3. Percent of time spent in hyperglycemia from 12 am to 6 am as a function of age and type of medication.

Finally to test the hypothesis that age and type of treatment may have interacting effects with respect to percentage time in the hyperglycemic state a third multiple regression was constructed (Table 5). The Interaction was not significant for either the early morning interval or for the daytime interval. Apparently, age and type of treatment have relatively independent influences on the percentage of time in the hyperglycemic state.

	% Time Hyperglycemic from 12 am to 6 am		% Time Hyperglycemic from 6 am to 6 pm	
Predictors	**Beta**	**R^2**	**Beta**	**R^2**
Hemoglobin A1c	0.31	0.09*	- 0.14	0.02
Age Group	0.23	0.04	-0.19	0.03
Medication Type	0.24	0.06*	-0.14	0.02
Age Group X Type	-0.50	0.01	- 0.47	0.01

Beta = Standardized Beta; Medication Type: Oral =1, Insulin =2

*p< .05; **p<.01

Table 5. Multiple Linear Regressions – Relationship Between the Interaction of Age X Medication Type (Oral, Insulin) and % Time Hyperglycemic

4. Conclusion

Results from this study demonstrate that both increasing age and the exclusive use of oral anti-hyperglycemic medications are associated with a lower percent of time spent in hyperglycemia during the early morning. On the other hand, as age increases, the opposite effect is exhibited during the daytime interval, namely a higher percent of time in the hyperglycemic state. In search for an explanation for these findings there is evidence from the animal literature that in older rats, glucose utilization by the brain, using autoradiography, tended to increase more slowly in the morning and decrease faster in the afternoon and evening (Wise et al., 1988). That is, glucose utilization is overall less effective during the day for older rats leading to elevated levels of blood glucose and possibly hyperglycemia during the day. Thus, glucose levels in older human subjects (≥65 years) compared to younger subjects (<65 years) appear to display a similar pattern as those found in the older rats. If the interspecies mechanism is similar, this would give some explanation to the pattern of increased percentage of diurnal hyperglycemia found in the older subjects with diabetes.

There was no interaction between age of patient and type of medication administered. Therefore, our findings showing that older people and people taking only oral medication exhibit less time spent in hyperglycemia during the early morning are two completely independent predictors of hyperglycemic episodes and do not influence each other.

Secondly, elevated HbA1c levels correlated with the percent time spent in a hyperglycemic state primarily during the early morning time interval. A study of Type II diabetics revealed that non-euglycemic states in the morning (pre-breakfast) and at night (bedtime) correlated with increased HbA1c levels. Therefore, patients whose glucose levels were not regulated well in the morning or late night tended to have poorer overall glycemic control as

measured by HbA1c. Perhaps the reason why the strongest association with HbA1c was "exerted" during the night (between the bedtime and pre-breakfast measurements) was due to the inability to effectively respond to extreme glucose values while asleep. Thus in the absence of an insulin injection (or comparable treatment) to correct for the elevated blood glucose levels, these patients may have an overall higher HbA1c. This indicates the importance of normalizing glucose levels overnight so as to avoid hyper and hypoglycemic states.

Future studies are needed to help account for the mechanisms behind both the age and percent time spent in hyperglycemia as well as the use of oral medication and percent time spent in hyperglycemia. Cortisol, for example, has been shown to promote the release of large amounts of glucose into the bloodstream as well as to block the absorption of insulin and it was shown that cortisol increases with age (Larsson et al., 2009). Therefore it would be beneficial to look further into this relationship as a means of explaining some of our results. It was also shown that the amount of REM sleep is reduced by about half in late life. This loss of REM sleep has been correlated with elevated cortisol levels throughout the day (Van Cauter et al., 2000). Increased cortisol elevates insulin resistance thereby promoting hyperglycemic episodes that may be reflected in older subjects with presumptive sleep difficulties.

Among the limitations of the present study is the absence of female subjects. Also many of the Type II diabetics recruited for this study were found to be taking insulin with or without oral medication. This led to treatment overlap between the diabetic types making it difficult to justify analysis based on type of diabetes, so instead the treatment modality was compared. This analytic strategy resulted in the elimination of 15 patients due to their treatment plan using both insulin and oral medications.

In summary, this continuous glucose monitoring study presents some novel observations into the relationship between hyperglycemia, advancing age and treatment type. While hypoglycemic episodes may also cause life-threatening situations, prolonged hyperglycemic episodes throughout the night, while asleep, will promote life-threatening sequellae and reduced quality of life. Although the complications of hyperglycemia may not be as instantaneously debilitating or as acute as hypoglycemia, more research is needed to prevent these episodes (Greene et al., 1992; Morello, 2007; Resnikoff et al., 2004). By understanding the pathophysiology behind circadian fluctuations of hyperglycemic episodes, physicians may be better able to help patients reduce the frequency and duration of these occurrences and thus reduce the complications that are associated with them.

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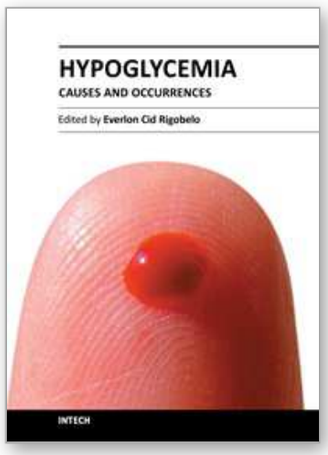

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Glucose is an essential metabolic substrate of all mammalian cells being the major carbohydrate presented to the cell for energy production and also many other anabolic requirements. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the glucose serum concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. This book provides an abundance of information for all who need them in order to help many people worldwide.

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