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Important considerations about the article pragmatic approach to the treatment of diabetes mellitus

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It's not knowing a lot, but knowing what's useful, what makes a man wise.

Thomas Willis

As it is well known, diabetes mellitus is a highly prevalent disease in the population worldwide. It also constitutes one of the main causes of mortality, and therefore, it should be considered a serious public health problem.

During the past few decades, the treatment of diabetes mellitus has received much interest from the medical and scientific community in general. The acquired knowledge of the disease is rapidly expanding, and the utilized therapeutic measures have been modified accordingly to reflect this increasing knowledge. For this reason and due to the continuously increasing data, the management of diabetes appears to have become more complicated. This makes us think that afflicted patients should necessarily be treated by a diabetes specialist.

Even though this might be desirable, we have to take into account that the number of patients is overwhelming and there are not enough specialized physicians to treat them all. In the majority of the cases, a general practitioner, a family medicine specialist, or an internal medicine specialist can appropriately manage these patients. Only in the presence of serious complications from the disease would we need to recur to a diabetes expert.

Over the past years, one of the most important contributions to the treatment of the disease was the demonstration that strict diabetes control is capable of avoiding all together or slowing down the development of the terrible chronic complications of the disease. We arrived at this conclusion through multiple studies in different regions of the world. However, the first landmark trial in the treatment of diabetes was a multicenter study in the United States known as diabetes control and complications trial, commonly known as DCCT.

It is the interest of our article to present a simple and practical approach to understanding the management of diabetes mellitus. Insulin is central in this management and everything else gravitates around insulin. Keeping this in mind allows us to comprehend the treatment as a whole better. This is the reason why we titled the article "*Pragmatic Approach to the Treatment of Diabetes Mellitus.*" We believe that with the implementation of the following advises, we can achieve, in the majority of cases, the so-called strict diabetes control.

Like Elliot P. Joslin (distinguished American diabetologist) said:

"*Education is not a part of the treatment of diabetes, education is the treatment*." In other words, the most important aspect when initiating diabetic control in a patient is to provide him with all of the information pertinent of the disease. In this way, the patient can actively be a part of the treatment.

In general terms, diabetes can be as good or as bad of disease as we want it to be. By this, we mean, that if the disease is adequately controlled, the majority of

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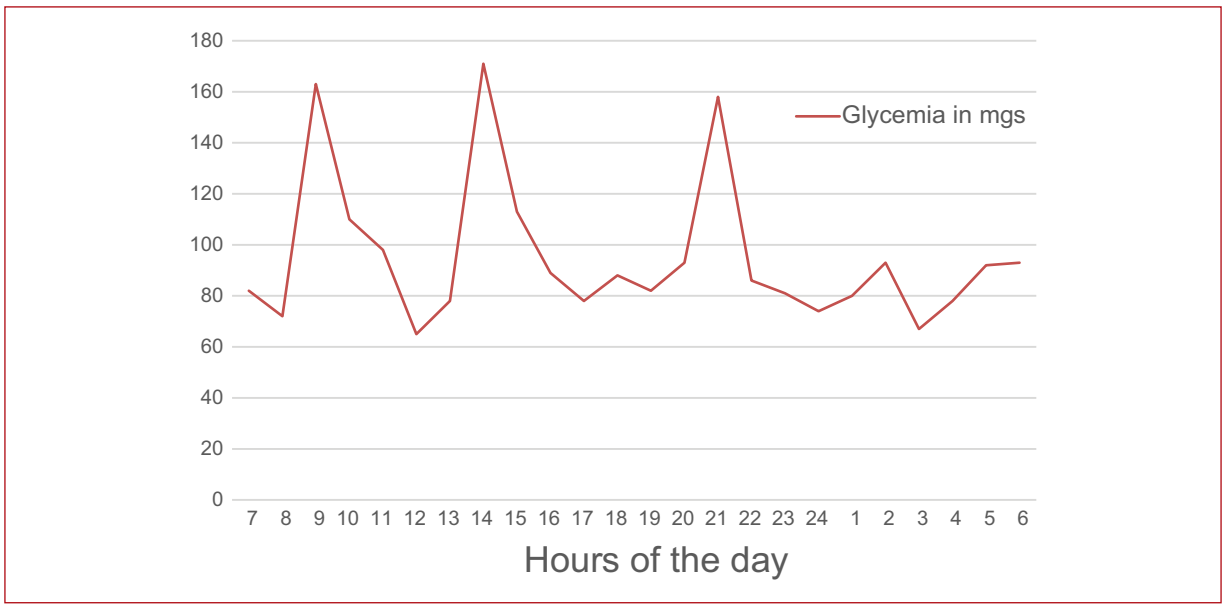

Figure 1. Glycemic curve during the 24 h of the day of a healthy person, 365 days/year all his life.

the patients could live practically the same number of years that they would have lived if they did not have the disease. Furthermore, they could enjoy a good quality of life during these years.

The key to achieving this control is precisely the education that the patient needs to be provided regarding his or her disease. After concluding the education process, the patient should be able to answer three questions correctly:

1. Diabetes control consists of what?
2. How do we achieve diabetes control?
3. How do we evaluate progression and control of the disease?

1. Diabetes control consists of imitating nature

If we analyze glycemic fluctuations over the course of 1 day in a healthy adult, we would observe that in the early morning hours (before breakfast), glucose oscillates within the accepted normal range (70-100 mg/dL). This level is maintained until after breakfast, at which point the level rises to around 140-160 mg/dL 1 h following food ingestion. The level then rapidly declines and reaches basal state 2 h after peaking. It fluctuates only mildly until lunchtime, at which point we can appreciate another peak that is slightly higher than the morning one (depending on the amount of food ingested). In general, it should not achieve levels higher than 180 mg/dL. It then again reaches basal state 2 h after peaking. It fluctuates mildly until dinner and the same phenomenon is repeated (Fig. 1).

These are the normal glycemic levels in a healthy adult during the 24 h of the day, 365 days/year, throughout all of his or her life. It is then of paramount importance that the treatment offered to the patient achieves glycemic ranges that closely resemble the healthy patient's levels. This is what we call imitating nature. Permanently achieving these levels are what is known as strict glycemic control. With these considerations, we answer the first question; this is what a good diabetes control consists of?

2. On the following question: how do we achieve diabetes control? The answer is simple: with insulin. This simplistic response needs to be further explained.

The main causation factors for the development of diabetes are the increase in hepatic glucose production, the deterioration of the production and secretion of insulin, and the development of peripheral insulin resistance[2]. These physiological changes frequently appear years before the clinical manifestations of the disease.

The final causation factor of diabetes is the lack of insulin activity at a cellular level. Therefore, the treatment should be aimed as a response to an intracellular insulin deficiency. The only treatment for diabetes is insulin therapy.

To understand this, we have to consider that diabetes progresses through three stages[3]. In the first clinical stage, the pancreas function is only mildly impaired; it still produces insulin, though not enough. In these conditions, if the patient is subjected to a good nutritional program combined with appropriate physical exercise

and weight loss (if appropriate), diabetes can be controlled in a relatively short amount of time because an extra load has been taken off the pancreas and its insulin reserves are now enough to normalize glycemic levels. This means that the disease has been controlled with the patient's endogenous insulin, which is doubtless the best insulin available.

If the physiopathologic problem continues and hepatic function declines further, hepatic glucose production increases with the simultaneous increase in peripheral insulin resistance. At this stage, lifestyle changes and weight loss are not enough to achieve glycemic control, and other therapeutic methods are required. These pharmacologic therapies achieve an enhanced endogenous insulin activity by different mechanisms of action. For example oral hypoglycemic agents like sulfonylureas which increase insulin secretion by direct action on Langerhans Islets, or thiozolidinediones which reduce peripheral insulin resistance for its action on different tissues. Metformin reduces hepatic glucose production (among other effects). Alpha-glucosidase inhibitors decrease intestinal glucose absorption in the initial portions of the digestive tract and, therefore, decrease glycemic levels. Meglitinides are capable of stimulating endogenous insulin production. Dipeptidyl peptidase-4 inhibitors by inhibiting this enzyme are capable of prolonging endogenous insulin activity.

Incretins are hormones produced normally in the digestive tract that has the capacity of stimulating insulin production and decreasing glucagon secretion. Incretin mimetics are now also used for the treatment of diabetes.

As we can observe, in the present day, there are innumerable pharmacologic agents available for the management of diabetes[4]. However, if they have one thing in common, it is that they all depend on the pancreas ability to produce some amount of insulin; in the last instance, it is this hormone that ends up achieving control of the disease. Most importantly, it is the patient's own insulin that ends up achieving control of the disease.

The third stage of the disease when the deterioration of the function has reached a degree, in which the pancreas does not produce any insulin or the levels of insulin are so low that patients do not respond to the pharmacologic agents previously discussed. To achieve control in this stage, exogenous insulin is required. This is why we insist that in every stage of the disease, the central element is always insulin.

3. How to evaluate progression and control of the disease? This is the last question that patients should be able to answer.

We obviously have to recognize that there is useful information obtained from a clinical history and physical examination. That means that patients recognize an overall feeling of wellbeing, furthermore,they may notice diminished thirst and urine volume as well as increase in physical strength and body weight. However, even though all this is important, we need more objective measures to help us asses the degree of glycemic control. The presence or absence of glycosuria or the levels of fasting or postprandial glucose are still useful tools. However, if we hope to achieve a strict glycemic control, and with this avoid or delay the chronic complications of diabetes, we need exact measurements that correlate well with disease progression and control. For example, glycosylated hemoglobin and especially capillary glucose levels as many times per day as necessary to ensure us that the glycemic fluctuations throughout the day resemble as much as possible those of a healthy person.

The determination of glycosylated hemoglobin is a very useful tool which can be repeated every 2 months. It is capable of providing us with a glycemic average over the few weeks before the measurement. However, it will not allow us to know with absolute certainty if the target glucose levels are being reached on a day-to-day basis. For this reason, the best method to ensure a tight glycemic control is the determination of capillary glucose multiple times per day.

It is a procedure that can be cumbersome for the patients as they have to be submitting to constant needle pricks, and this is something that not everyone is willing to do. It can also represent a financial burden, which is another obstacle for its implementation. As part of the solution for these problems, we can recur to less frequent glucose determinations, sometimes while fasting and sometimes postprandial. We can find different schemes that adjust to each patient preference and financial possibilities.

We hope that with the information shared in these pages, we have provided you with a simple and practical approach for a successful treatment of diabetes in the majority of your patients.

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