Review

Blood glucose levels in diabetic and non-diabetic subjects^{*}

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Most, if not all, diabetologists are convinced, on the basis of indirect evidence which has been accumulated over the decades that the microangiopathic and neurological complications of diabetes are primarily dependent on the duration and extent of chronic hyperglycaemia [1–5]. Hyperglycaemia is the necessary factor in the development of these complications even if other, secondary factors, sometimes responsive to treatment, such as blood pressure levels, smoking, protein intake, with or without genetic predisposition, may modulate its expression [6]. However, as emphasized by Krolewski et al. [7] and Mogensen [8] it is the degree (and duration) of hyperglycaemia which remains the most important aetiological factor in predisposed groups of patients.

Before we are able to detect with accuracy on an *individual* basis the subjects at risk from diabetic complications, blood glucose control will be of paramount importance because, as emphasized by Rothman [9]:

“Identification of all the components of a given sufficient cause is unnecessary for prevention, in that blocking the causal role of but one component of a sufficient cause renders the joint action of the other components insufficient and prevents the effect.”

Among the advice given to an insulin-treated diabetic patient that which is related to glucose control is aiming to try to normalize blood glucose levels. Regarding blood glucose control we will discuss briefly the following points: What are “normal”, fasting and post-prandial blood glucose levels? What are fasting and post-prandial blood glucose levels of insulin-treated diabetic patients? What are the limiting factors to the normalization of blood glucose levels in diabetic patients? How high is high? (harmfulness of hyperglycaemia), and How to advance present-day treatment?

“Normal” fasting blood glucose levels

It is wise, firstly, to question the meaning of the word normal. Table 1 lists, according to Murphy [10–12], the situations in which the word “normal” is used and the preferable term (the choice of which depends on the goal).

Amidst the seven meanings proposed by this methodologist one is of particular importance for the epidemiologist: i. e. the reference value, namely that obtained from a population considered healthy and serving as reference. Another is probably much more useful in individual medical practice and is that which defines the norm as non-pathogenic and the abnormal as dangerous to one's health. A famous example well illustrates these points: when a group of European researchers, working on urinary bilharzia, asked the chief of a sub-tropical village to gather all his subjects presenting abnormal urines in the main square, only three appeared, their urine was perfectly limpid and the “normal” population was that which had red urine and was ill.

Fasting plasma glucose levels are unimodally distributed within apparently non-diabetic adult populations except in a few highly inbred communities in Arizona and the South Pacific. In the French telecommunications adult employee population of 3220 adults studied by my colleague D. Simon and his collaborators [13] 95% of the values obtained regardless of sex, and age, are below 106 mg per 100 ml i. e. 5.8 mmol/l (Table 2). According to Gaspard [14] the distribution of blood glucose values in a general population is asymmetric with a tail towards higher values and is true for both sexes.

Fasting plasma glucose in apparently non-diabetic subjects tends to rise with age [13–15]. The younger the subjects the more their blood sugar levels are distributed below 5.5. mmol/l (Table 2).

Fasting glycaemia is lower in pre-menopausal women than in men [13, 16] (Table 2). We have also shown that natural oestrogen administration decreases fasting blood glucose levels in young healthy men [17].

The fact that pre-menopausal women have lower fasting blood glucose levels than men is an important fact to

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Table 1. Murphy's seven meanings for "normal"

Paraphrase	Where used	Preferable term
1. Probability function (bell-shaped curve)	Statistics	Gaussian
2. Most representative of its class	Descriptive sciences	Average, median, mod.
3. Commonly encountered in its class	Descriptive sciences	Habitual
4. Most suited to survival	Genetics, operations research	Optimal, "fittest"
5. Carrying no penalty	Clinical medicine	Innocuous, harmless
6. Commonly aspired to	Politics, sociology	Conventional
7. Most perfect of its class	Metaphysics, esthetics, morals	Ideal

[10–12]

Table 2. Fasting plasma glucose by age, sex and menopausal status in the adult telecom population

	<i>n</i>	Mean	SD.	Min	P1%	P5%	P10%	P25%	P50%	P75%	P90%	P95%	P99%	Max
All subjects	3220	90.13 5.01	9.59 0.53	67.00 3.72	73.00 4.06	77.00 4.28	80.00 4.44	84.00 4.67	90.00 5.00	95.00 5.28	102.00 5.67	106.00 5.89	117.00 6.50	265.00 14.72
Men	1560	92.80 5.16	9.95 0.55	70.00 3.89	76.00 4.22	80.00 4.44	83.00 4.61	87.00 4.83	92.00 5.11	98.00 5.44	103.00 5.72	108.00 6.00	120.00 6.67	265.00 14.72
Women	1660	87.62 4.87	8.51 0.47	67.00 3.72	72.00 4.00	76.00 4.22	78.00 4.33	82.00 4.56	86.00 4.78	92.00 5.11	100.00 5.56	103.00 5.72	112.00 6.22	140.00 7.78
Non menopausal	1207	86.41 4.80	7.62 0.42	67.00 3.72	71.00 3.94	76.00 4.22	78.00 4.33	81.00 4.50	85.00 4.72	90.00 5.00	96.00 5.33	101.00 5.61	110.00 6.11	125.00 6.94
Menopausal	453	90.82 5.05	9.83 0.55	70.00 3.89	73.00 4.06	77.00 4.28	80.00 4.44	83.00 4.61	90.00 5.00	97.00 5.39	103.00 5.72	110.00 6.11	121.00 6.72	140.00 7.78
All subjects														
Age	<i>n</i>	Mean	SD.	Min	P1%	P5%	P10%	P25%	P50%	P75%	P90%	P95%	P99%	Max
20–29	854	86.32 4.80	7.03 0.39	68.00 3.78	71.00 3.94	75.00 4.17	77.00 4.28	82.00 4.56	86.00 4.78	90.00 5.00	95.00 5.28	100.00 5.56	104.00 5.78	114.00 6.33
30–39	855	89.54 4.97	8.32 0.46	67.00 3.72	73.00 4.06	78.00 4.33	80.00 4.44	84.00 4.67	89.00 4.94	94.00 5.22	100.00 5.56	103.00 5.72	109.00 6.06	183.00 10.17
40–50	673	90.89 5.05	8.47 0.47	68.00 3.78	75.00 4.17	79.00 4.39	81.00 4.50	85.00 4.72	90.00 5.00	96.00 5.33	102.00 5.67	106.00 5.89	114.00 6.33	132.00 7.33
50 +	838	94.01 5.22	12.02 0.67	71.00 3.94	74.00 4.11	79.00 4.39	82.00 4.56	87.00 4.83	93.00 5.17	100.00 5.56	107.00 5.94	111.00 6.17	128.00 7.11	265.00 14.72
Men														
20–29	479	88.72 4.93	6.75 0.38	71.00 3.94	75.00 4.17	78.00 4.33	81.00 4.50	84.00 4.67	88.00 4.89	92.00 5.11	98.00 5.44	100.00 5.56	107.00 5.94	114.00 6.33
30–39	462	92.15 5.12	8.23 0.46	70.00 3.89	76.00 4.22	81.00 4.50	83.00 4.61	88.00 4.89	92.00 5.11	96.00 5.33	101.00 5.61	104.00 5.78	111.00 6.17	183.00 10.17
40–50	270	94.54 5.25	8.29 0.46	77.00 4.28	78.00 4.33	82.00 4.56	84.00 4.67	89.00 4.94	94.00 5.22	100.00 5.56	104.00 5.78	109.00 6.06	118.00 6.56	132.00 7.33
50 +	349	97.94 5.44	13.63 0.76	74.00 4.11	77.00 4.28	84.00 4.67	86.00 4.78	90.00 5.00	97.00 5.39	103.00 5.72	110.00 6.11	117.00 6.50	139.00 7.72	265.00 14.72
Women														
20–29	375	83.25 4.63	6.14 0.34	68.00 3.78	70.00 3.89	74.00 4.11	76.00 4.22	79.00 4.39	83.00 4.61	87.00 4.83	91.00 5.06	94.00 5.22	100.00 5.56	104.00 5.78
30–39	393	86.47 4.80	7.33 0.41	67.00 3.72	72.00 4.00	76.00 4.22	79.00 4.39	81.00 4.50	85.00 4.72	90.00 5.00	95.00 5.28	101.00 5.61	109.00 6.06	117.00 6.50
40–50	403	88.45 4.91	7.68 0.43	68.00 3.78	72.00 4.00	78.00 4.33	80.00 4.44	84.00 4.67	88.00 4.89	92.00 5.11	99.00 5.50	104.00 5.78	111.00 6.17	119.00 6.61
50 +	489	91.20 5.07	9.81 0.55	71.00 3.94	73.00 4.06	77.00 4.28	80.00 4.44	84.00 4.67	90.00 5.00	97.00 5.39	103.00 5.72	110.00 6.11	122.00 6.78	140.00 7.78

Unpublished data from Simon et al. [13]
Values are given in mg/dl; in mmol/l

Table 3. Venous plasma glucose levels (mg/dl and mmol/l) in 244 pregnant non-diabetic women at 33–37 weeks of pregnancy and no diabetic risk factors

	Mean	SD	Range	
Fasting	80	8	55–108	98.4% < 100 mg/ml
	4.4	0.4	3.0–6	< 5.5 mmol/l
Post meal	90	16	60–150	97.5% < 126 mg/ml
(not-standardized)	5	0.8	3.3–8.3	< 7 mmol/l

Unpublished data from C. Tchobroutsky and M. Vray, Maternity University Hospital of Port-Royal (Paris) and INSERM U. 21 (Villejuif)

consider when carrying out a fasting test period for the diagnosis of spontaneous hypoglycaemia. During a fasting state blood glucose levels decrease more in pre-menopausal women than in men or post-menopausal women [16].

Fasting plasma glucose values in non-diabetic pregnant women have also been studied. Unpublished data from the Maternity University Hospital of Port-Royal have shown that 98.4% of the fasting values are below 5.5 mmol/l in healthy pregnant women with no diabetic risk factors at 33–37 weeks gestation (Table 3). Farmer and colleagues studied 917 pregnant non-diabetic women at 32 weeks gestation: 97.5% of the values observed were below 5.2 mmol/l [18]. Thus, it appears that in non-diabetic pregnant women fasting blood glucose values are much lower than those often considered as “normal” at least on the highly specific criteria required by some authors for the determination of glycaemic abnormalities during pregnancy [19].

As is perfectly known, reference values include, when the distribution is unimodal, some subjects in the upper percentiles who are already ill or at high risk of becoming ill. The upper tail of these unimodal distributions sometimes shows surprisingly high values in supposed “healthy” populations used as reference [14, 15]. Although this might be due to bias in the selection of the subjects.

Epidemiologists try to set up classifications which are simply tools for longitudinal studies or for comparison between groups and populations. In borderline cases definitions and classifications must not be interpreted as clues for individual diagnosis of diabetes or non-diabetes. Unfortunately despite constant warnings, particularly from the WHO expert committee [20], these arbitrary figures, neither sacrosanct nor eternal, are currently used for clinical practice or clinical studies leading to misleading titles and conclusions. The important issue is to know whether a slightly increased blood glucose level (e.g. above the 95th percentile in young subjects or above the 97.5th in elderly patients of the reference population) is the hallmark of diabetes or just one of the several markers (risk factors) of possible future diabetes mellitus as are other better known markers.

“Normal” post-prandial blood glucose levels

Few studies have been devoted to defining normal post-prandial blood glucose values. When they were done they usually concerned very small groups of subjects and were

restricted to the midday meal with the exception of a 1976 study [21] and two non-standardized very large epidemiological studies [22, 23].

In 1970 we performed a study concerning 8 healthy subjects and 16 diabetic patients who consumed a standardized 880 kcal meal containing 90 g of carbohydrate [22]. All these normal, 20- to 40-year-old, adult subjects maintained their maximal post-prandial blood glucose levels on this standardized meal below 6 mmol/l 2 h after the beginning of the meal.

We later studied the variations in glycaemia 45 to 120 min following a midday non-standardized meal in 110 non-diabetic subjects 45 of whom were apparently healthy and 65 who presented with non-metabolic diseases [23]. The increments in post-prandial plasma glycaemias were extremely small.

Non-standardized post-prandial blood glucose levels rise with age according to the formula: second hour blood glucose = $0.516 \times \text{years} + 88.2$ (in mg/dl) [23].

From the Port-Royal Maternity Hospital data it appears that post-prandial plasma glucose levels remain at a low level during pregnancy, even close to delivery since 97.5% of the values remain below 7 mmol/l between 1 h 30 min and 2 h post cibum (Table 3).

Blood glucose levels in insulin-treated patients

Despite our efforts directed towards the ideal achievement of normalised blood glucose levels it is obvious that in Type 1 (insulin-dependent) diabetic patients, treatment remains far from optimal and blood glucose levels, in terms of means, never really attain the values observed in the reference populations.

a) *Pregnancy* might be the best example to show, on the one hand, the progress we can achieve with routine treatment and, on the other, our limitations. This condition also serves to draw attention to an area in which there is general consensus as to the need for the best possible glycaemic control [24]. From unpublished data on 389 pregnancies in Type 1 diabetic patients conjointly followed with the Maternity Hospital of Port-Royal it appears that between 1971 and 1977 fasting and post-prandial blood sugar levels were never normalized in terms of means and that after 1978, despite technological advances in diabetology and obstetrics the values have, if anything, become worse: the blood glucose levels at entry and at 32 weeks were as follows: *during the 1971–1977 period* mean fasting plasma glucose (mmol/l, mean $\pm$ SD) was 8.2 ± 4.3 in the first trimester and 6.3 ± 2.8 at 32 weeks. Post-prandial levels (1 h 30 min to 2 h after the beginning of the main meal) were 6.6 ± 3.3 and 5.8 ± 2.5 , respectively. *In the second period*, the following values were found: fasting: 8.1 ± 4.2 in the first trimester; 8.0 ± 2.8 at 32 weeks; post-prandial: 7.9 ± 2.8 in the first trimester and 7.1 ± 3.1 at 32 weeks. These differences were significant for fasting plasma values at 32 weeks ($p < 0.001$), post-prandial levels in the first trimester ($p < 0.001$) and at 32 weeks ($p < 0.001$). This may in fact be due to recent technological advances which have released both doctors and pa-

Table 4. Amniotic fluid concentrations of glucose, insulin and C-peptide related to gestational age

Duration of pregnancy (weeks)	< 32	32 to 35	≥ 36
Glucose (mg/100 ml)			
Normal	30 (1)	24 ± 2 (10)	22 ± 4 (13)
Diabetics	– (0)	53 ± 6 (18)	42 ± 6 (27)
	–	$p < 0.01$	$p < 0.05$
Insulin (μU/ml)			
Normal	2 (1)	6 ± 1 (11)	7 ± 1 (15)
Diabetics	– (0)	15 ± 2 (17)	25 ± 7 (27)
	–	$p < 0.01$	$p < 0.01$
C-peptide (ng/ml)			
Normal	1.6 (1)	1.4 ± 0.3 (10)	1.3 ± 0.2 (14)
Diabetics	– (0)	2.5 ± 0.3 (15)	2.3 ± 0.4 (21)
	–	$p < 0.05$	$p < 0.06$

Number of subjects shown in parentheses. Results given as mean ± SEM [31]

Table 5. Values of mean fasting (F) and post prandial (PP) blood glucose and haemoglobin A_{1c} (HbA_{1c}) levels for the insulin dependent diabetic patients

Centers <i>n</i> =	W 95	X 63	Y 51	Z 44
FBG mg/dl	146 ± 74	149 ± 78	235 ± 117	227 ± 10
mmol/l	8.1 ± 4.1	8.3 ± 4.3	13.0 ± 6.5	12.6 ± 5.5
PP BG mg/dl	175 ± 85	215 ± 105	205 ± 103	–
mmol/l	9.7 ± 4.7	11.9 ± 5.8	11.4 ± 5.7	–
HbA _{1c} %	7.7 ± 1.7	8.2 ± 1.4	10.6 ± 2.0	11.3 ± 1.8

Unpublished data from the Damad Study [34]

tients from anxiety. Despite these changes in glycaemic control beneficial effects have been obtained in premature deliveries and in the number of Caesarian deliveries without change in perinatal mortality. This is due to the desirability of carrying the pregnancy as close as possible to full term. However, even when corrected by the later term, it appears that although mean birthweights have risen significantly the numbers of malformations remain the same.

Examples from the literature indicate that even in the most motivated of health-care systems, the percentage of well controlled patients is feeble apart from a few experimental studies, where enormous efforts have been made by practitioners such as Lois Jovanovic and her colleagues [25] or Reversi et al. [26]. In general what is obtained is a mean glycaemic control which is at best, 30 to 40% over reference values. Data from Chicago [27] where definition of good control is empirical and reasonable, but where normoglycaemia is not achieved, showed that at the beginning of the pregnancy only 27% of pregnant women had what was considered to be good glucose control. This number rises to 62% from week 32 onwards. The author's aim was to show that the frequency of large for gestational age infants was

conditioned by the metabolic control achieved before week 31 and not by that of the last trimester. Data presented by the late Ivo Drury in his Banting lecture [28], based on glycated haemoglobin values (given along with their reference values) showed that 38% of the women followed in Dublin had HbA_{1c} values within the normal reference range throughout the third trimester. The higher the glyco-haemoglobin values the heavier the children were (birthweight being corrected by gestational age).

These data, including ours, cover the last 15 to 20 years. But results are no better in a recent multicentre study done in the USA [29].

With reference to some consequences of this lack of normalisation of blood glucose in terms of means during pregnancy Farmer et al. [18] remark upon the fact that in reference populations where the fasting blood glucose levels and other parameters are in the lower normal range, birthweight and subcutaneous skin thickness in particular depend closely on "normal" maternal blood glucose levels. As British authors have pointed out, birthweight values are distributed along Gaussian distributions in reference as well as in diabetic populations [30]. One can probably extend this causal relationship between glycaemia and weight from children of non-diabetic mothers to those of diabetic women who, due to our sub-optimal therapeutic conditions, are statistically and inexorably overweight for their term. Whether it is dangerous or not, whether it increases the number of Caesarian deliveries or induces increased mortality in these children are questions I will not discuss but it is highly probable that all these risks are linearly related to maternal blood glucose levels without clear pathogenic cut-off points.

Table 4 shows the data we obtained in 1980 [31] concerning changes in the fetus as reflected in changes in amniotic fluid from diabetic and non-diabetic mothers. The glucose concentration in amniotic fluid of the diabetic patients was markedly higher than in the control subjects, before and after 36 weeks of gestation. This was responsible for an increased insulin-secretion in the child assessed on C-peptide levels in the amniotic fluid which reached twice those of control subjects. There was a close correlation between C-peptide and glucose concentrations in the amniotic fluid ($p < 0.05$) and the infant's birthweight ($p < 0.01$) (even after correction for gestational age) ($p < 0.05$).

b) *Blood glucose levels in the general non-pregnant Type 1 diabetic population.* Data from Düsseldorf, Vienna and Bucharest [32] showed that HbA_{1c} values in Type 1 diabetic patients obtained with routine, yet highly-structured teaching and care systems were identical to those observed in so-called highly intensive research conditions. Thus, improvements are possible when health-care management is structured and when methods using either multiple injections or continuous insulin infusion by pumps are implemented. The best that can be achieved in terms of means is as in pregnancy Hb values 30 to 40% above mean reference values. Less than 10 years ago we carried out a cross-sectional study in in-

Fig. 1. Post prandial blood sugar (right) and plasma insulin (left) levels in 38 non-diabetic ● and 30 Type 1 (insulin-dependent) diabetic subjects ○. Values are mean $\pm$ SEM. Values for the 14 patients treated by 3 daily injections of insulin are given separately Δ . NS = non significant; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; (based on data from Tchobroutsky et al. [36])

Fig. 2. Plasma levels of glucose, human growth hormone (HGH) and insulin before, during and after exercise in seven healthy ○ and six insulin-treated ● diabetic men. Values are means $\pm$ SEM. Before and during exercise the mean plasma insulin values are significantly higher in the diabetic than in the healthy subjects at times: -10, 2.5, 5, 10, 15 and 20 min. ** = $p < 0.01$, *** = $p < 0.001$. (From G. Tchobroutsky et al. [39])

sulin-treated diabetic out-patients [33]. Only 19% of all the diabetic patients had HbA_{1c} levels less than 3 SD above the mean reference value. But the percentage of subjects in whom HbA_{1c} values could be considered as acceptable was 33% in those receiving three daily injections (usually fast-acting regular insulin before each meal associated with intermediate insulin either at bedtime or with the evening meal). As for post-prandial blood glucose values collected randomly 1 to 2 h after the beginning of a non-standard meal, it appeared that they were very low ("normal") in those who had received regular insulin before the meal. All that is needed is to prescribe the regular insulin! Table 5 shows data from four centres which have participated in a multicentre European trial [34]. Great differences can be seen between the centres in mean fasting and post-prandial glycaemia as in Hb levels.

Current limitation to blood glucose control in insulin-treated patients

We are aware of the obstacles facing progress in blood glucose control in Type 1 diabetic patients with our current routine treatments: they are psychological, social and educational in nature but also reflect our inability to mimic native insulin physiology. Indeed, insulin is injected in the wrong place and as has often been said at the wrong time, in the wrong way and in the wrong quantities. Whatever insulin-resistance there may be it appears that the major obstacle is our difficulty or inability to restore physiological portal insulin levels.

After a meal control of glycaemic excursions in non-diabetic subjects depends, in my opinion, essentially on the insulin concentrations obtained in the portal vein and on the speed with which this peak of insulinaemia is reached. After the pioneering work of Blackard and Nelson [35], we studied in 1973 [36] non-diabetic subjects (and also Type 2 (non-insulin dependent)) diabetic patients as we benefitted at that time from the development of per-umbilical access to the portal vein. In non-diabetic subjects, peripheral blood insulin levels decline as early as 30 min following a meal, with an equal fall in portal vein blood levels where concentrations were at least 2 to 4 times higher than the peripheral levels from 60 min onwards.

In Type 1 diabetic patients treated with insulin it is obvious that for physical reasons the systemic venous concentrations achieved by the peripheral administration of insulin are the same as those obtained in the portal vein since insulin is not injected into the portal system. In 1970 and 1973 we attempted to deal with this problem indirectly [22, 36] by studying the circulating peripheral exogenous plasma insulin levels in Type 1 diabetic patients. We took well controlled patients treated for less than three or, more often, one month who had previously been hospitalized with severe insulin deprivation presenting with diabetic coma or severe ketosis and in whom the absence of anti-insulin antibodies [37] allowed an estimate of exogenous circulating peripheral insulin levels. Blood glucose levels in treated diabetic patients were extremely high after meals, although less so in those who received three injections of regular insulin per day, but insulin levels were still higher in diabetic patients than in normal subjects, in spite of high concomitant blood sugar levels (Fig. 1). It seems unnecessary, but not to be excluded, to invoke insulin resistance to explain this phenomenon (in fact insulin resistance in Type 1 diabetes is reversible after treatment [38]). In view of the fact that peripheral insulin levels are *also* the portal insulin levels of these treated diabetic patients these portal levels are quite obviously insufficient compared to those of non-diabetic subjects.

In order to obtain normalisation of blood glucose levels, it is important to obtain in peripheral venous blood, both before and after meals, insulin levels at least two to three times as high as those observed in the peripheral blood-stream of control subjects as shown in 1974 [39], when we undertook a study to evaluate the secretion of growth hormone during exercise (Fig. 2) (which of course was normal when blood glucose levels were also normal).

Table 6. Some pioneering studies on the use of regular insulin

Johnsson	1960	Forsham	1967
Lawrence	1963	Pedersen	1967
Lukens	1965	Metz et al.	1967
Aubertin	1965	Earl	1968
Oakley et al.	1966	Service et al.	1970
Chabanier (in Deuil)	1967	Rull et al.	1970
Tutin et al.	1967	Spathis	1970
		Vining and Strong	1972

[45]

What physiology teaches us is that therapy is far from being just that, i.e. physiological, not to mention the peripheral hyperinsulinism we induce.

Danger of high blood glucose levels

Epidemiological studies have shown that in Type 2 diabetic patients blood glucose levels below 7.8 mmol/l on fasting and 11.1 mmol/l after meals may not be harmful to the kidney or the retina [40, 41].

Mogensen [42] has emphasised that it could be possible that lesions may remain minimal when HbA_{1c} levels are kept within 4 SD of the mean. In a recent longitudinal study from the USA, Chase and colleagues [43] have shown that the risk of developing micro-albuminuria at any age, or the risk of developing any preoccupying retinopathic lesions was proportionally much lower when mean HbA_{1c} values were less than 10% above the upper normal range. The risk increases rapidly with higher but not necessarily catastrophic Hb levels.

As mentioned above in the field of obstetrics there is probably no threshold to the deleterious effect of glycaemia but rather a linear relationship between blood glucose levels and macrosomia even in healthy normal women. This may be true for miscarriage as shown by Mills et al. [44] and probably also for congenital malformations.

How to progress in routine conditions of treatment

So I believe, as do many other diabetologists, that it is very important to improve blood glucose control, as well as other parameters such as blood pressure, in diabetic patients. Even if ideal control cannot be achieved the lower the blood glucose level the better. Perhaps in the near future it will be possible to identify all those diabetic patients at risk of developing complications and focus on them our greatest efforts.

There is now a growing trend, to use regular fast-acting insulin several times a day in conjunction with intermediate insulin, for the night using an insulin pen-injection system. This regimen has been advocated over the last 30 years (Table 6) [45]. At least post-prandial glucose levels can be improved by using regular insulin injections before each meal [23].

The use of regular insulin and the structuring of care and teaching have induced, as we have shown [46] among others, better equilibrium and better results in terms of life-style for diabetic patients. Hypoglycaemic episodes

are less frequent and quality of life has been improved by energetic management. Due to the limitations we are faced with, we know that insulin treatment remains imperfect. Short-acting insulins and/or the use of intra-nasal administration of the hormone, even if of some help, will not allow per se physiological treatment. But the impossibility of attaining "normal" plasma glucose levels is not a reason for pessimism. Better is better than bad.

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