

**GLYCOSYLATED HAEMOGLOBIN (G-Hb) AS A
PARAMETER IN DIABETIC CONTROL AND ITS
POSSIBLE ROLE IN PATHOGENESIS OF
DIABETIC RETINOPATHY**

THESIS

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I N T R O D U C T I O N
&
A I M O F T H E W O R K

Aim of the Work :

Since most diabetic complications are due to unusual glycoprotein occurring in diabetes (Beissminger and Spiro, 1970; Koenig et al., 1976a and Bunn et al., 1978), and as glycosylated haemoglobin is a glycohaemoglobin, its increase in diabetic patients may be correlated to the diabetic complications. The aim of this work is an attempt to correlate the level of glycosylated Hb with criteria of diabetic control and incidence of complications especially diabetic retinopathy, since recent publications (Trivelli et al., 1971; Koenig et al., 1976a and Bunn et al., 1978) are pointing to a rise of HbA_{1c} as a possible aetiological factor, besides other factors, through local hypoxia in the retina.

Introduction :

In 1958 Allen et al. discovered a new component of normal human haemoglobin which was referred to as glycosylated haemoglobin (G-Hb).

Glycosylated haemoglobins are blood glucose components accumulated within the living red blood cells by the attachment of glucose to the N-terminal valine of the

B chain of HbA molecule. This attachment occurs slowly, non enzymatically, and continuously through the 120 days of normal mature human red blood cells life in the peripheral circulation.

The glycosylation occurs through a stable linkage which is rearranged into an irreversible state, so, it remains attached and detectable as such, until the life of R.B.C. is ended.

Proliferative retinopathy commonly leads to an advanced diabetic eye disease, and a permanent visual loss because of persistent vitreous haemorrhage, macular traction, extensive retinitis proliferans and retinal detachment. (Beetham, 1963).

In those patients with proliferative retinopathy, oedema and/or ischaemia of the macula causes loss of acuity in a greater number of patients than the vitreous haemorrhage does (although the severity of visual loss is often worse when is caused by vitreous haemorrhage) (Liang and Goldberg, 1980).

Patho-Histology :

The terminal arterioles show characteristic alterations at their points of origin including hyaline thickenings, corkscrew coiling and narrowing of the lumen. (Ashton, 1963); while U-shaped capillary loops and varicose dilatations are also common, mainly on the venous parts of the capillaries but occasionally also towards the arteriolar ends (Ashton, 1973 and Bloodworth, 1962). In their ultrastructure, however, the capillaries show peculiar features (Duke-Elder & Dobree, 1967).

The basement membrane is frequently thickened and its different layers are separated by debris sometimes interspersed with lipid droplets, and a typical change is a loss of intramural pericytes and endothelial cells. In scattered areas of the diabetic retina a pattern of "ghost" capillaries can be made out, occluded functionless vessels represented only by their basement membrane, possessing neither pericytes nor endothelial cells (the so-called "mesodermal bridges"). Adjacent to these the neighbouring functional capillaries may lose their intramural pericytes or their endothelial cells and are frequently the site of saccular aneurysms. In close association with these are distended, tortuous and highly cellular capillaries which may possibly be "shunt" vessels developed to provide alternate dilated channels to maintain the circulation (Cogan and Kuwabara, 1963).

Micro-aneurysms; first described by Mackenzie and Nattleship (1877), are not confined to this disease but are particularly common; Ashton (1963) demonstrated by means of Neoprencast and Indian ink injections the enormous numbers in which they may occur; several may develop in a single capillary giving an effect of beading. They may

assume a saccular form arising from the side of a capillary or an ampulliform shape, in their early stages their walls may be thin so that erythrocytes may pass through them (Bloodworth, 1962) , but as they develop they tend to acquire thickened laminated coats formed by the deposition of PAS-positive material, while at a later stage they thrombose and their lumina are occluded by laminated hyaline material (Duke-Elder and Dobree, 1967). In diabetic rats maintained for 9-12 months, microthrombi were observed in the various sized retinal vessels at histological and ultrastructural level. The microthrombus was mainly composed of aggregated platelets and fibrin strands . (Tatsuro et al., 1981).

The Haemorrhages: in diabetic retinopathy may be found in all layers of the retina, but occur preferably from the capillary plexus in the outer plexiform layer where they are circumscribed by the density of the nervous elements; these are thus fairly small and round, but larger sheet like haemorrhages in the inner layers are much less common and may pass through the internal limiting membrane and spread in the subhyaloid space .

New Vessels : are commonly seen, first in the retina itself where the new-formation appear as closely-packed tufts where in the process of looping is clearly seen, and when the vessels have ruptured through the internal limiting membrane, they grow as flat pannus-like networks between the retina and the vitreous, when again looping is a prominent feature. (Duke-Elder and Dobree, 1967).

The Exudates: of diabetic retinopathy are characteristic. The typical "waxy" exudates form in the first instance in the outer plexiform layer of the retina (Ballantyne and Loewenstein, 1943) and in Henle's fibre layer in the macular area (Walter et al., 1957) without any relation to the neighbouring blood vessels, flat preparations show that they have finger-like processes winding through the outer plexiform layer but as they enlarge all the retinal layers are eventually invaded and deposits are also found as a localized sheathing along the adventitia of the larger vessels. The fatty material is partly intracellular and partly extracellular. The extracellular deposits are amorphous masses which stain readily. The intracellular fat is contained in large rounded cells

with small nuclei (glitter cells), phagocytic in function and microglial in nature, stuffed with fat and occurring in clustures.

The lipids in the waxy plaques result from the polymerisation of unsaturated fats and are in the chemical form of ceroid (wax-like) material. The origin of the lipids has long been a matter for speculation. The abnormal concentration of lipid frequently found in the plasma of diabetics led earlier workers to believe that they were deposits from the blood stream but the fact that these waxy plaques are always found in areas of neuronal degeneration suggests that they are breakdown products of degenerate nervous tissue which is gradually removed by the phagocytic action of the microglial cell (Bloodworth, 1962).

The Soft Exudates or Cotton-Wool Patches : On the other hand, are typical capillary infarcts containing cytoid bodies of the same nature as those which occur in hypertensive and other conditions.

Degenerative Changes in Retinal Nervous Tissue: are a prominent feature of diabetic retinopathy, for large numbers of the neurons degenerate, both the cells and their dendrites

become swollen and finally fragmenting (Walter, 1957. and Bloodworth, 1962). In severe cases, there is a great reduction in the number of ganglion cells, and a corresponding diminution of the nerve-fibre layer and in the advanced stages there is a marked gliosis especially in the inner layers of the retina. (Duke-Elder and Dobree, 1967).

(VI)

FACTORS IMPLICATED IN THE
GENESIS OF DIABETIC RETINOPATHY