HIGH CARBOHYDRATE DIET PLUS GREEN BEANS (PHASEOLUS VULGARIS,L) IN THE TREATMENT OF DIABETES MELLITUS AND ITS PREVENTION OF VASCULAR COMPLICATIONS.

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Abstract

The number of patients registered at the Diabetic Clinic of the Dr. Soetomo Hospital during 16 years (1964-1979) amounted to 4976, consisting of 3748 (75.3%) treated with oral hypoglycemic drugs, 396 (8.0%) treated with insulin and 832 (16.7%) treated with diet only. Based on the kinds and the price of durgs available, oral hypoglycemic agents such as tolbutamide (1139 = 30.4%) and chlorpropamide (661 = 17.6%), glibenclamide (1725 = 46.0%), gliclazide (163 = 4.4%), and gliquidone (60 = 1.6%) have been prescribed since 1964,1973 1976 and 1979 respectively.

A comparative study, using a crossover design (Tjokroprawiro, 1978), has been carried out on 260 cooperative diabetic out-patients, to investigate whether the B-diet (68% cbh, 20% fat, 12% protein) was metabolically and socio-economically better than the A-diet (50% cbh, 30% fat, 20% protein). The results of the study showed that the B-diet is better than the A-diet; interestingly, the serum cholesterol level was significantly 31.75 mg% ($p < 0.001$) lower on the B-diet than on the A-diet after a one week dietary period.

It was speculated that HDL cholesterol would be higher on the B-diet, and consequently the incidence of diabetic vascular complications might be lowered; hence, the B-diet has been widely prescribed for the treatment of patients with diabetes mellitus in Indonesia since 1978.

Recent studies with crossover designs demonstrated that the B-diet plus 600 grams green beans (Phaseolus Vulgaris, L) daily, showed significant hypoglycemic (Tjokroprawiro et al, 1980) and hypolipidemic (Budhiarta et al, 1980) effects on poorly controlled diabetic patients after a one week dietary period.

It has been postulated that gliclazide is an oral hypoglycemic drug which is able to reduce platelet adhesiveness and aggregation, is able to antagonize adrenaline vasoconstrictive hyperreactivity in the vessel wall, and which has also a fibrinolytic effect at hypoglycemic doses.

We conclude that the combination of the high carbohydrate diet (the B-diet), green beans, and gliclazide may be of real value in the therapeutical implication attempting to prevent or minimize vascular complications for non-insulin dependent diabetic patients.

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INTRODUCTION

The number of patients registered at the Diabetic Clinic of Dr. Soetomo Hospital during 16 years (1964-1979) amounted to 4976, consisting of 3748(75.3%) treated with oral hypoglycemic drugs, 396 (8.0%) treated with insulin and 832 (16.7%) treated with diet only.

Based on the kinds and the price of drugs available, oral hypoglycemic agents such as tolbutamide (1139 = 30.4%), gliclazide (163 = 4.4%), and gliquidone (60 = 1.6%) have been prescribed since 1964, 1973, 1976 and 1979 respectively.

It was really impressed in the Diabetic Clinic that diet appears to be an essential part of diabetic treatment, and it was postulated that one of the important causes of the failures is the poor adherence to the A-diet (Western in type, 50% cal. carbohydrate, 30% cal. fat and 20% cal. protein).

Hence, we prescribe a B-diet (68% cal. carbohydrate, 20% cal. fat and 12% cal. protein), a new dietetic regimen for diabetic patients, adapted to the eating habit of the Indonesian people.

In Indonesian rural areas traditional medicines are still widely used.

The green bean or Phaseolus Vulagris is easily avaibable in Indonesia, and it was reported by Tanuwidjaja et al. (1977) that green bean showed a hypoglycemic effect on normal subjects.

However, no study on the effect of green beans on blood sugar and lipids levels of diabetic patients has been reported.

Being faced with such problems, two comparatives studies using a randomized crossover design were carried out, to investigate whether the B-diet was metabolically better than the A-diet, and whether green beans had metabolic effects on diabetic patients.

It has been postulated that gliclazide is an oral hypoglycemic drug which is able to reduce platelet adhesiveness and aggregation, is able to antagonize

adrenaline vasoconstrictive hyperreactivity in the vessel wall, and which has also a fibrinolytic effect at hypoglycemic doses.

If such studies were fruitful, such findings may be of great medicinal value to the Indonesian patients or the other ones with diabetes mellitus.

PATIENTS AND METHODS

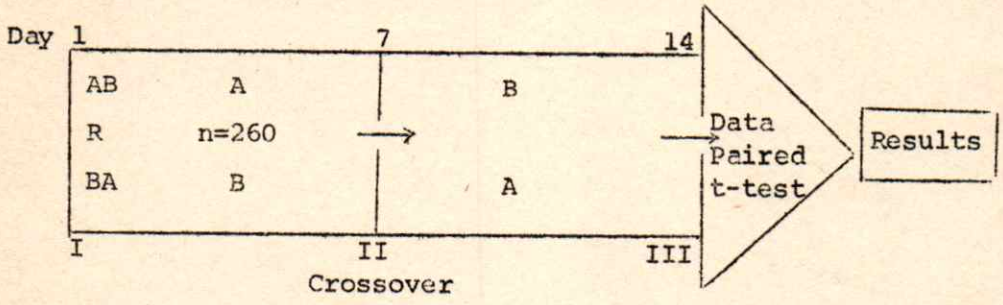
INVESTIGATION I (Tjokroprawiro, 1978)

Investigation I is a prospective and comparative study using a randomized crossover design (the A-diet vs the B-diet).

Compositions of the A-diet and the B-diet are as follows :

	The A-diet	The B-diet
Carbohydrate	: 50% of calories	68% of calories
Protein	: 20%	12%
Fat	: 30%	20%
P.S. ratio	: 0.6	1.0
Cholesterol intake	: 500 mg per day	100-150 mg per day
Distribution and meal frequency	: 30%, 40%, 30%	20%,10%,25%,10%,25%,10%.

Protocol : randomized crossover design (Rocket System, Tjokroprawiro 1978)



A = The B-diet

R = Randomized

AB = The AB sequence

BA = The BA sequence

n = Total number of patients (well controlled)

B = The B-diet

I,II,III = Points where the blood were drawn for B.S., Chol., and T.G. measurements

B.S. = Blood sugar

Chol. = Cholesterol

TG = Triglycerides

The experimental patients consist of 200 non insulin dependent and 60 insulin dependent diabetic - outpatients who have been well controlled and cooperative. The A-diet and the B-diet are isocalorically maintained. The dietary period for each type of diet is one week. Blood sugar level (fasting and 2 hours post breakfast), serum cholesterol and triglyceride levels were used as parameters.

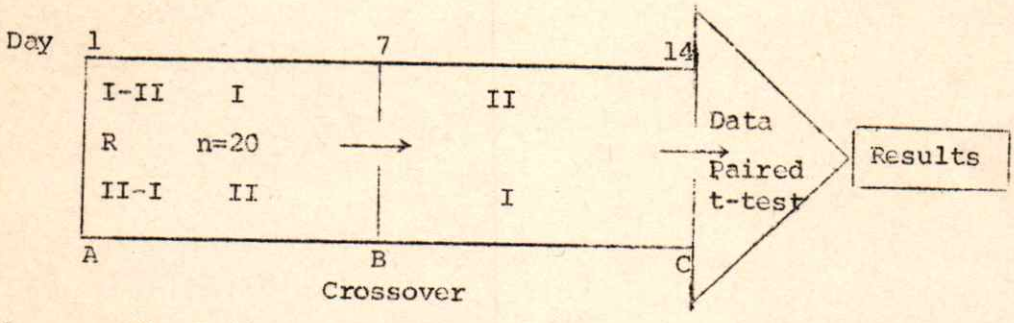
Paired t-test was used for statistical analysis.

Patients were excluded if, during the period of the investigation, undergoing conditions that affect the blood levels of the parameters.

INVESTIGATION II (Tjokroprawiro, 1980)

Investigation II is a prospective and comparative study using a randomized crossover design (Diet I vs Diet II)

Protocol : randomized crossover design (Rocket System, Tjokroprawiro 1978)



I = The B-diet

R = Randomized

I-II = The I-II sequence

II-I = The II-I sequence

n = Total number of patients (poorly controlled)

II = The B-diet plus 3x200 grams green beans

A,B,C = Points where the blood were drawn for BS, Chol. and TG measurements

BS = Blood Sugar

Chol. = Cholesterol

TG = Triglyceride

In this investigation we selected 20 poorly controlled non insulin dependent diabetic-outpatients who have not been treated yet and cooperative (no hypo-

glycemic agents were used in this study.

The criterion of the poorly controlled patient is, if the average blood sugar level is higher than 175 mg%.

Average blood sugar can be obtained by dividing the sum of fasting blood sugar and 2 hour postprandial blood levels by two.

Cooked green beans are given three times daily (from 3x200 grams raw green beans).

The data were statistically analized

RESULTS

INVESTIGATION I : TABLE 1

TABLE 1. AVERAGE VALUES OF FASTING BLOOD SUGAR (FBS), 2 HOUR POST BREAKFAST BLOOD SUGAR (2hP.B.), SERUM CHOLESTEROL (Chol.) AND TRIGLYCERIDE LEVELS (TG) OF 260 PATIENTS (the A-diet vs the B-diet).

Diets / Change	FBS mg %	2h.P.B. mg %	Chol. mg %	T.G. mg %	Patients (n)
$\bar{A}$	92.75	126.08	269.78	125.77	260
$\bar{B}$	89.93	122.07	238.03	124.18	260
Change	2.82	4.01	31.75	1.59	
P	0.02*)	0.02*)	<0.0001*)	0.60	

*) Significant

Patients : well controlled DM

INVESTIGATION II : TABLE 2

TABLE 2. AVERAGE VALUES OF AVERAGE BLOOD SUGAR (B.S.), SERUM CHOLESTERAL Chol.) AND TRIGLYCERIDE LEVELS (TG) OF 20 PATIENTS (DIET I VS DIET II)

Diets / Change	BS mg %	Chol. mg %	TG mg %	Patients (n)
I	227.98	155.79	132.29	20
II	194.90	148.96	124.19	20
Change	33.08 *)	6.83 *)	8.10 *)	
p	<0.01	<0.05	<0.05	

*) Significant

Patients : poorly controlled DM

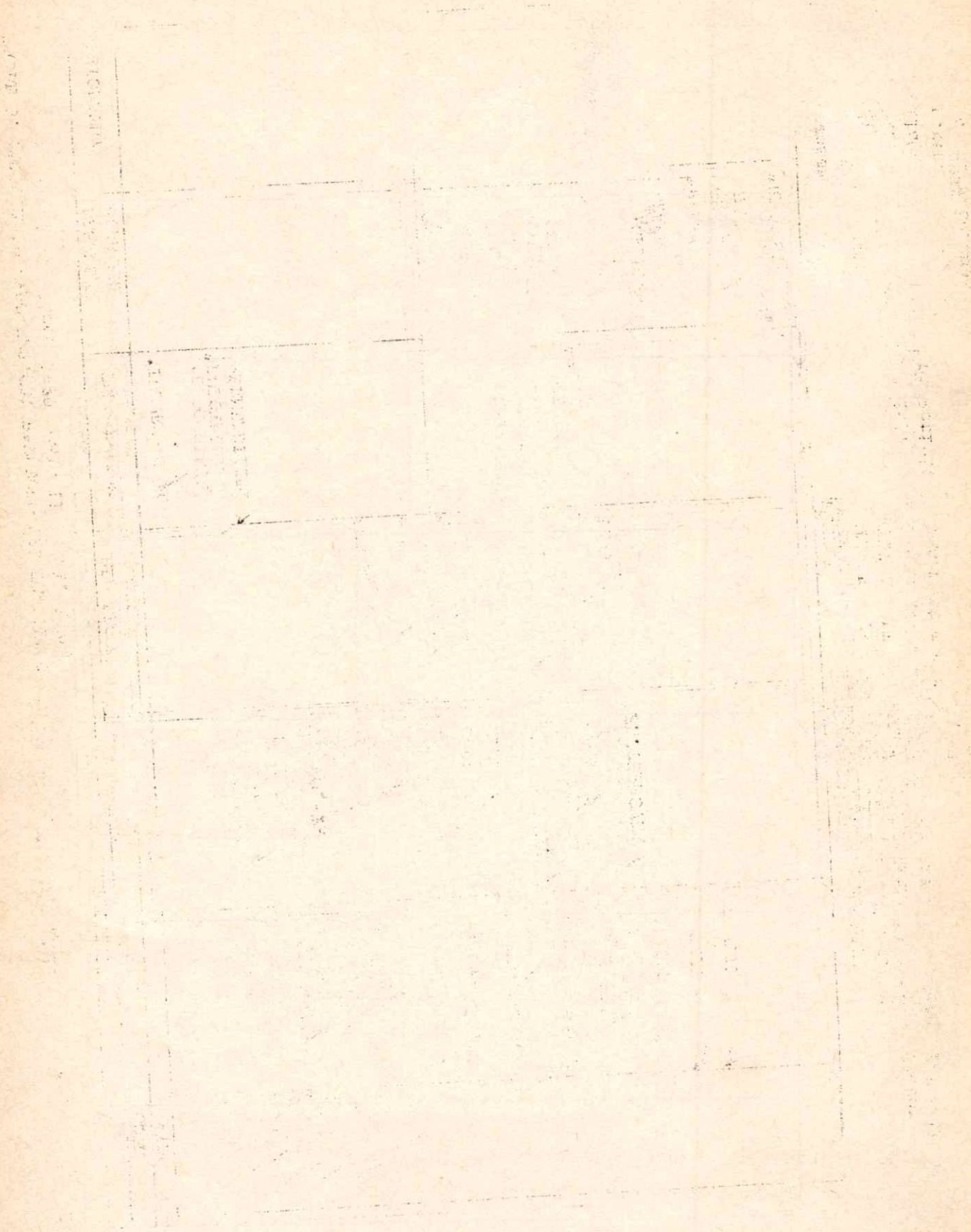
$$B.S. = \frac{FBS + 2h.P.B.}{2}$$

TABLE 3. SUMMARIZED HYPOTHETICAL PATHOGENETIC FACTORS IN DIABETIC MACRO AND MICRO ANGIOPATHY (Desnoyers et al. 1979, Bloom 1979, Colwell et al. 1979)

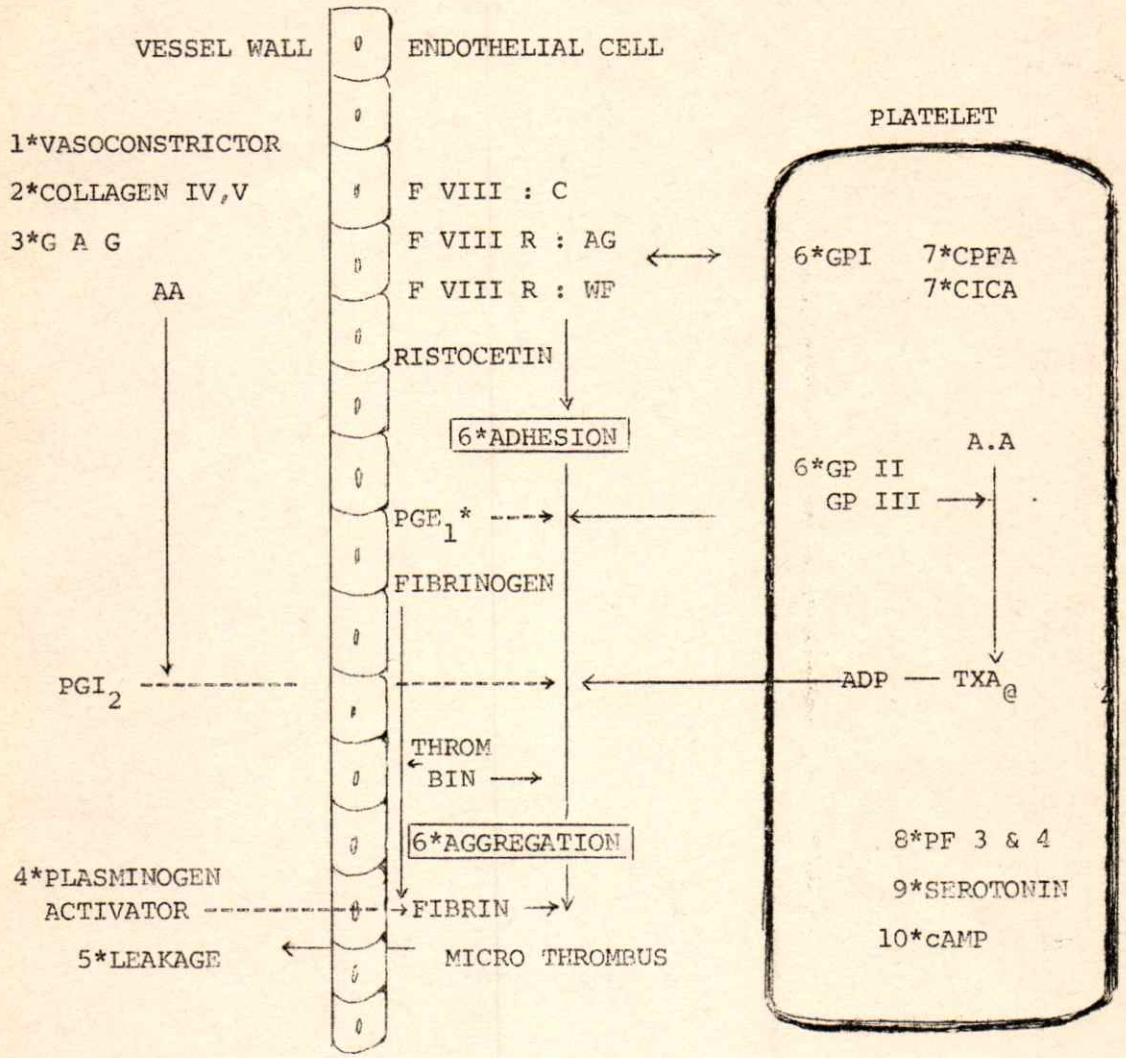
ANGIOPATHY	BASEMENT MEMBRANE	ENDOTHELIUM	RED BLOOD CELLS	PLATELETS	PLASMA	BLOOD LIPIDS
MACROANGIO-PATHY		*INJURY-DAMAGE ↗ *ENDOTHELIAL PERMEABILITY ↗	*HB A_{1c} ↗ *2,3 DPG ↙ *ART. MUSCLE CELL PROLIFERATION *LIPID ↗ $-O_2$ UNLOADING ↙ *E DEFORMABILITY ↙	*GLYCOPROTEIN I,II,III ↗ *AA-PG_2-TXA_2-AXIS ↗ *PGG_2 ↗ *PG_E ↗ *PF 3 & 4 ↗ *CPFA ↗ *CICA ↗ *PL. ADHESION ↗ *PL. AGGREGATION ↗ *PL.TURNOVER ↗	*BTG ↗ *PLASMAVISCOSITY ↗ *α_1-ACID GLYCOPROTEIN ↗ *COMPLEMENT ↗ *FIBRINOGEN ↗ *CERULOPLASMIN ↗ *HAPTOGLOBIN ↗ *C-REACTIVE PROTEIN ↗ *F VIII: C ↗ *F VIII R : AG ↗ *F VIII R : WF ↗	*LDL ↗ *VLDL ↗ *HDL ↙ *CHOL. ↗ *TG ↗
MICROANGIO-PATHY	*COLLAGEN IV,V ↗ *CYSTIN ↙ → LEAKAGE *GLYCOPROTEIN ↗ *G A G ↙ *THICKENING, LEAKAGE *PLASMINOGEN ACVATOR ↙ *REVERSIBLE?	*DEATH-REGENERATION *PGI_2 ↙				

GAG = Glycosaminoglycans
GP = Glycoprotein
PF = Platelet Factor
CPFA = Contact Product Forming Activity
CICA = Collagen Induced Coagulant Activity
ART = Arterial
BTG = Beta Thromboglobulin

F VIII : C = procoagulant factor VIII
F VIII R : AG = Factor VIII Related Antigen
F VIII R : WF = Factor VIII Related Willebrand factor
Collagen IV, V are secreted by diabetic endothelial cell to basement membrane
P.L. = Platelet

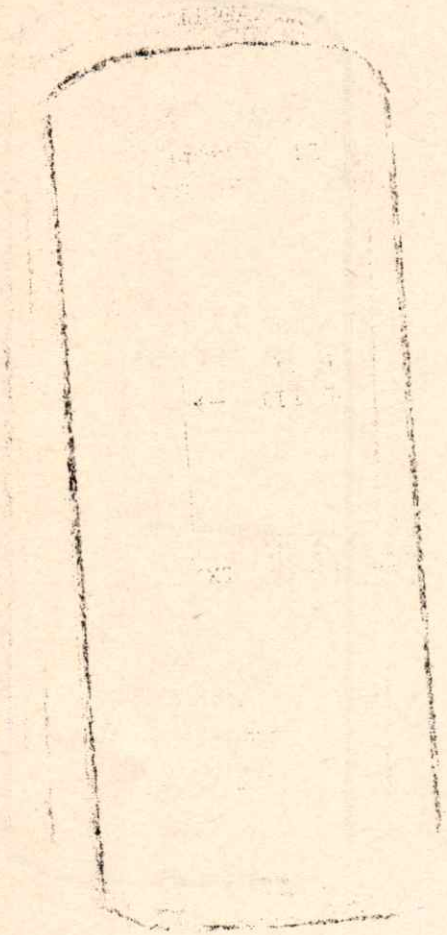


THE DIAGRAMATIC HYPOTHESIS OF THE PATHOGENESIS OF DIABETIC MICROANGIOPATHY
(Duhault et al. 1979, Desnoyer et al. 1979, Bloom 1979, Colwell et al. 1979)



*) Sites of action of gliclazide (hypothesis)

1. Restore microvascular sensitivity to adrenaline to a normal level.
2. Decrease endothelial cell secretion of Collagen IV and V to basement membrane
3. Increase the GAG containing coat of the endothelial cells
4. Release the plasminogen activator (anti microthrombus formation).
5. Restore capillary per meability
6. Reduce platelet adhesiveness and aggregation (interaction with GPI and GPII, III)
7. Inhibit the release of CPFA and CICA
8. Inhibit the excretion of PF 3 & 4
9. Inhibit the liberation of serotonin
10. Increase intraplatelet cyclic AMP.



DISCUSSION

A. INVESTIGATION I

B. INVESTIGATION II

C. METABOLIC EFFECT OF GLICLAZIDE

INVESTIGATION I

In this study, significant differences in both fasting and 2 hour post breakfast blood sugar levels of the A-diet and the B-diet were found although such differences were too low (FBS = 2.82 mg%, $p = 0.02$, whereas 2hP.B. = 4.01 mg% $p = 0.02$) and clinically unmeaningful. Such findings are consistent with the results reported by Brunzell et al (1970, 1971), Anderson (1973) and Tjokroprawiro et al. (1977). Such low hypoglycemic effects of the B-diet was likely caused by the fact that the initial levels of the blood sugar were entirely normal. Probably, the hypoglycemic effect of the B-diet would be apparent if, the subjects of the study were the hyperglycemic ones.

Interestingly, the serum cholesterol level was significantly 3.75 mg% lower on the B-diet than on the A-diet (TABLE 1, $p < 0.0001$).

Prersumably, the B-diet leads to less efficient reabsorption of bile acids (Whyte et al., 1973), and an increased excretion of bile acids ensues (Portman et al., 1955; 1958).

However, there is no evidence that any of factors provided for the B-diet i.e. reduction of dietary fat, substitution of polyunsaturates for saturates, low in cholesterol intake, high in fiber, frequent meal, and high carbohydrate consumption, was more successful than any of the others in lowering the serum cholesterol level. It was suggested that combined metabolic interaction of all such factors might have given the results.

As seen in TABLE 1, there is no difference in serum triglyceride level of patients between the two diets ($p = 0.66$).

The nature of carbohydrate used in this study may have been significant in preventing the commonly reported hyperlipidemia response. This speculation is supported by the findings of some authors who found no increase in fasting serum triglyceride levels in diabetic patients when compared on diets low and high in carbohydrates but sugar free (Stone et al.,1963; Weinsier et al.,1974). Of interest in this connection, is that vegetables of different types and meal distribution which are provided for the B-diet, may probably play a role. The ingestion of carbohydrates high in fiber might slow down the proces of digestion and absorption, hence, there is a mild but prolonged increase in blood glucose with a small insulin response.

As synthesis of triglycerides in the liver is influenced by insulin, such variations in insulin secretion might be of importance in preventing the occurence of hypertriglyceridemia.

INVESTIGATION II

Green beans really consist of fibres and bean pods. It is postulated that bean pods contain an insulin-like substance.

Much recent interest has been shown in treating diabetics with high fibre or fibre-supplemented diets to decrease post prandial hyperglycemia.

As seen in TABLE-2, irrespective of the sequence of diets, Diet II is apparently more effective to decrease blood sugar levels of poorly controlled diabetic patients than Diet I.

The average blood sugar level during Diet II is significantly 33.08 mg% lower than that during the Diet I period ($p < 0.01$).

Eventhough the decreases in serum cholesterol (6.83 mg%, $p < 0.05$) and triglyceride levels (8.10 mg%, $p < 0.05$) during Diet II are statistically significant, however, such differences are clinically unmeaningful.

There is no indication which of the factors belonging to the green bean, i.e. fibres or the insulin-like substance or other, is more succesful in lowering blood sugar and blood lipid levels.

It is perhaps of great importance that the considerable effect of absorption and transit time during green bean consumption was the most effective factor in decreasing post prandial glucose concentration and, also the sharp fluctuation of insulin secretion, in which the latter was responsible for blood lipids level. As seen in TABLE I, the B-diet showed an apparent hypocholesterolemic effect.

Goulder et al (1978) documented the beneficial effect of dietary fiber on glucose tolerance in diabetic individuals.

Finally, it is speculated that combined effect of green beans and high carbohydrate diet (the B-diet) appears to show an increased efficiency of peripheral glucose utilization and to show a hypolipidemic effect, or green bean consumption may potentiate the metabolic effect of a high carbohydrate diet (the B-diet). Hypothetically, the hypolipidemic effects of green beans will be clinically significant if such studies were carried out on patients with hyperlipidemia.

However, as far as metabolic balance study is concerned, an analysis of the hypoglycemic and hypolipidemic effects of green beans is of real importance for clinical reasons.

C. METABOLIC EFFECT OF GLICLAZIDE

See The DIAGRAM

Duhault **et** al (1979) summarized that by chronic gliclazide administration to diabetic rats, this hypoglycemic agent was shown to restore the microvascular sensitivity to adrenaline to a normal level, and the suppression of the capillary occlusion ensued.

Beneath the endothelium is the basement membrane and sub-endothelium.

The nature of the basement membrane is uncertain : it does not seem to consist of typical collagen fibrils, but contains complex glycoproteins and collagen-related materials. Bloom et al (1979) reviewed that types IV and V Collagens appeared to be associated with basement membrane structures and it might be secreted by the endothelium.

Gliclazide may decrease the Collagen IV and V content of the basement membranes. As reviewed by Duhault et al (1979) that the concentration of collagen increased, while the concentration of GAG (glycosaminoglycans) decreased in the skin of diabetic animals.

A decrease in the GAG containing coat of the endothelial cells could be responsible for abnormal functions of the endothelial surface.

It is possible that GAG may regulate the transport of lipoproteins accross the arterial wall, and it is suggested that the variations in the susceptibility of the arterial wall to injury are mediated by alterations in the content of GAG in the vascular wall. This might explain the increased entry of lipoproteins in the atherosclerotic aorta.

It has been also noticed that the anticoagolant activity in the intima is a function of the concentration of aortic acidic GAG.

Current studies using streptozotocin-induced diabetes revealed a decrease in the metabolism of the GAG of the skin in diabetic mice, which could be reversed with daily gliclazide administration.

This increase in GAG could be ascribed to both increased synthesis and decreased degradation and further study is needed to elucidate this effect.

It was postulated that the diabetic patients have reduced fibrinolytic activity, and such condition in responsible for the mural thrombus formation.

Approximately 20% of diabetics would appear to have a decrease in vascular

plasminogen activator levels. Desnoyers et al (1979) reviewed that gliclazide was capable of increasing the release of this activator by more than 80%. Duhault et al (1979) believed that as it was shown in diabetic rats gliclazide was able to decrease the microvascular permeability and restore the capillary permeability.

Bloom et al (1979) stated that both micro and macro angiopathy involved interaction of blood vessels, platelet and plasma factors which might be altered in diabetes.

Platelets may influence the development of angiopathy by two distinct but interrelated properties, i.e. adhesion and aggregation (see The DIAGRAM)

Adhesion involves : 1. a subendothelial component thought to be collagen

2. F VIII : C, F VIII R : AG, F VIII R : WF, Ristocetin co-factor

3. Platelet Membrane Glycoprotein I (GPI)

Agregation, which may be triggered by adhesion, involves the stimulation of the platelet arachidonic acid (A.A), thromboxane pathway (T X A_2) and the release of dense body ADP (See The DIAGRAM).

TXA_2 and ADP mediate aggregation by platelet membrane Glycoprotein II and III (GP II, GP III), but aggregation is inhibited by the vascular prostaglandin PGI_2 and also inhibited by PGE_1 in which the latter is secreted by endothelial cells. The main roles of fibrinogen in micro thrombosis are probably as the immediate precrusor of fibrin and as an important factor which influences plasma viscosity and the rheological characteristics of blood; thrombin is a potent platelet aggregant, whereas plasminogen activator is anti microthrombus formations. Increased platelet adhesiveness and aggregation, in addition, an increase in the liberation of platelet thrombogenic constituents, PF 3 and 4, fibrinogen levels, as well as an increase in the levels of factors, i.e.

F VIII:C, F VIII R:AG, F VIII R:WF, are frequently seen in the diabetics (Desnoyers et al, 1979).

It had been shown that gliclazide had an inhibitory effect upon the platelet adhesiveness and aggregation in both rat and man. Gliclazide showed strong inhibitory properties on the release of CPFA (Contact Product Forming Activity), CICA (Collagen - Induced Coagulant Activity), PF3 and 4, and serotonin; gliclazide also inhibits the synthesis of glycogen and stimulates the activity of adenylcyclase, that contributes to an increase in intraplatelet cyclic AMP levels and in the vessel wall, in which the latter is important factor in the prevention of the metabolism of PGI_2.

CONCLUSIONS

The B-diet is metabolically better than the A-diet. Serum cholesterol level of the B-diet is 31.75 mg% lower than that of the A-diet.

No hypertriglyceridemia is found with the B-diet although it is a high carbohydrate diet.

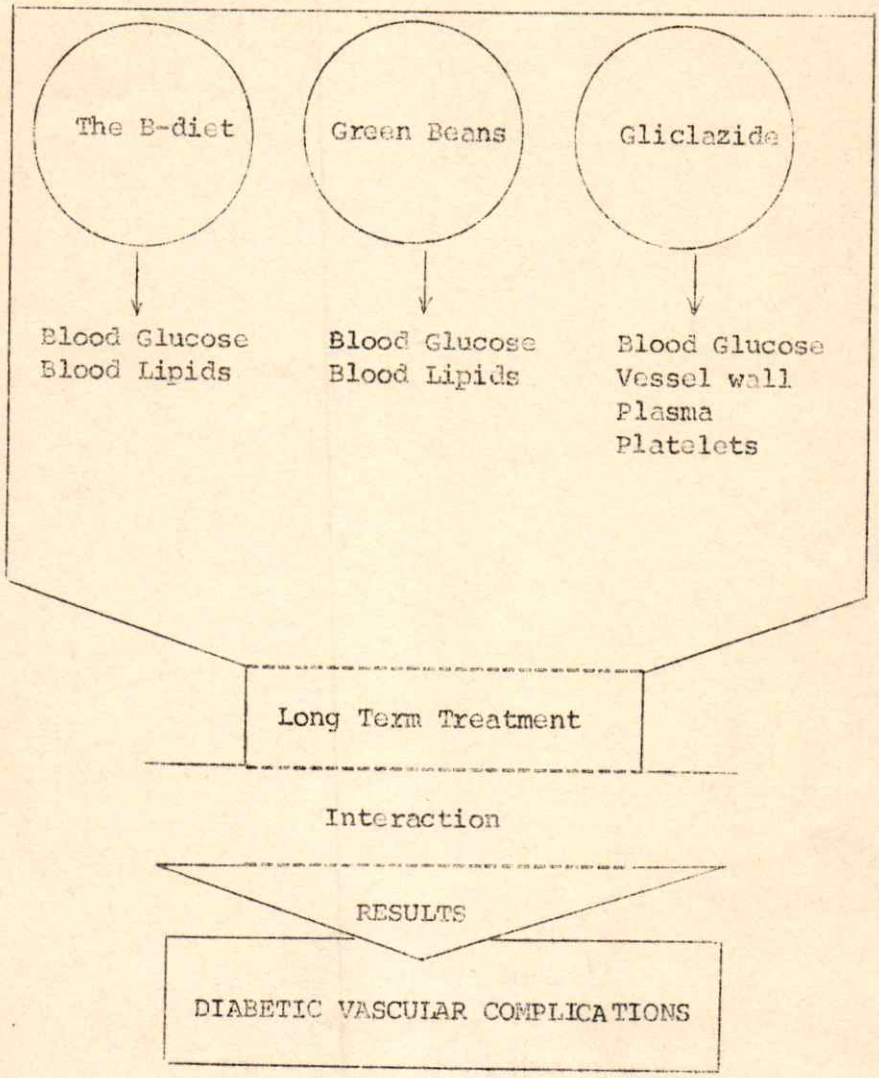
Green beans have a potent hypoglycemic (33.08 mg% in one week, $p < 0.01$) and, probably, hypolipidemic effects in patients with poorly controlled diabetes.

It is specualted that the two main effects of the B-diet may bring a hope of the increase in the HDL cholesterol and the low incidence of diabetic angiopathy ensues.

Sites of action of gliclazide as an anti-adhesive, anti-aggregant, and fibrinolytic agents which brings hopes of preventing the disorders of diabetic microangiopathy are located in the vessel wall, plasma and platelets.

Hypothetically, we suggest that the combination of longterm consumption of the B-diet, green beans, and gliclazide may be of real value in the therapeutical implication for non insulin dependent diabetics attempting to prevent or minimize the diabetic vascular complications.

Such a hypothesis can be schematically drawn as follows :



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High carbohydrate diet plus green beans (phaseolus vulgaris,L) in the treatment..
Tjokroprawiro,A.

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	U. Airlangga	20-9-83