Prostaglandin metabolism and intraocular pressure

NAVA NAVEH-FLOMAN AND MICHAEL BELKIN

From the Maurice and Gabriela Goldschleger Eye Research Institute, Tel Aviv University Sackler Faculty of Medicine, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel

SUMMARY The plasma lipid alterations characteristic of essential fatty acid deficiency (EFAD) generally appear one to two weeks after the initiation of fat free parenteral nutritional (PN), and may be associated with a reduction in prostaglandin (PG) formation. In the present study the relationship between exclusion of fat from the diet and changes in intraocular pressure (IOP) and PGE₂ plasma levels were studied in 28 patients. The results indicated that three weeks after the omission of dietary fat a significant reduction in IOP levels occurred which persisted throughout the follow-up period of 7 (SD 1.2) weeks. Plasma PGE₂ levels were also significantly reduced in patients on fat free PN for three weeks as compared with levels measured while patients were on a fat containing diet. This clinical observation is not yet understood and might be related to changes exerted by fatty acid deficiency.

Patients on fat-free parenteral nutrition (PN) may show the alterations in plasma lipid pattern characteristic of essential fatty acid deficiency (EFAD) as early as a week or two following initiation of the diet.¹⁻³ These changes involve a decrease in plasma levels of linoleic and arachidonic acids, and a significant increase in 5.8.11 eicosatrienoic acid.¹ The clinical manifestations of EFAD, desquamative dermatitis, hair loss, thrombocytopenia, and poor wound healing,² appear later in the course of this disorder.^{1,3}

Decreased prostaglandin (PG) production in EFAD may occur as a result of the reduction in arachidonic acid and the increase in 5.8.11 eicosatrienoic acid serum levels, since the latter is a potent inhibitor of PG synthesis and the former is the main substrate of PG production.^{4,5} PGs are mainly known for their mediatory role in inflammation in most organs,⁶ including the eye.^{7,8} Likewise it is well established that exogenous and endogenous PGs can give rise to acute elevation of intraocular pressure (IOP).⁹⁻¹² However, when applied in low doses PGs cause a prolonged reduction in IOP.¹³⁻¹⁶

The present study was undertaken to investigate the relationship of fat free nutrition, PGE₂ plasma levels, and IOP.

Subjects and methods

The subjects were 18 female and 10 male patients

Correspondence to Dr N Naveh-Floman.

aged 21 to 60 years who were on fat free PN. The age distribution and the diagnosis which necessitated the fat free PN are given in Table 1.

Fat free PN was the sole source of alimentation of all 28 patients for an average period of 7 ± 1.2 weeks (mean $\pm$ SD). The diet consisted of a mixture of crystalline amino acids, hypertonic glucose, electrolytes and vitamins. Later, fat supplementation (intra-lipid 10%, containing a mixture of essential fatty acids) was added for further 9 ± 2.1 weeks.

Though patients involved in this study were suffering from major illness, owing to the daily high calorie input made possible by the PN some were gaining weight, while none lost weight. Likewise there was

Table 1 Distribution of patients on PN according to age, sex, and diagnosis

Age (yr)	Sex		No. of patients
	Female	Male	
21-44	5	3	8
45-59	7	6	13
60 and over	5	2	7
Total			28
<i>Diagnosis</i>			
Ulcerative colitis			5
Crohn's disease			7
Neoplastic diseases			11
Diverticulitis			1
Lymphoma			4
Total			28

no fall in systemic blood pressure in these patients while they were on fat free diet. Supplementation of fat in these patients did not affect their general health, blood pressure, or body weight.

During the study the ophthalmologist involved was unaware of the diagnosis of the patient or his diet.

The IOP was measured at the bedside under topical anaesthesia with benoxinate hydrochloride 0.4% and a Schiøtz tonometer, with both 5.5 and 10.0 mg weights. The average of six measurements, three with each weight, was taken, and the deviation for each set of three measurements did not exceed 10–15%. All measurements were performed on all patients by the same ophthalmologist at the same time of day (between 10 and 12 am). Scleral rigidity was calculated for each patient by means of the paired Schiøtz tonometer reading as described.¹⁷ Patients with gross signs of inflammation or other ocular pathology were excluded. Measurements were made weekly—before the patients were started on the fat free PN, during the fat free PN, and after the patients received fat supplementation.

PGE₂ plasma levels were determined in 14 patients by radioimmunoassay of a PGE₂ metabolite (13,14-dehydro 15-keto PGE₂) using a specific antiserum.¹⁸

Blood samples for PGE₂ analysis were drawn into glass tubes containing EDTA (3.7×10^{-3} M final concentration) and indomethacin (10^{-6} M final concentration). They were then centrifuged at 2000 g for 15 minutes at 40°C. The plasma fraction was isolated, frozen, and stored at -70°C. Blood samples were drawn three weeks after fat free PN was initiated and then after three weeks of fat supplementation of the diet.

Data were statistically evaluated by Student's *t* test.

Results

The effect of dietary fat on IOP is shown in Table 2. Ocular pressure was significantly reduced on the

Table 2 Effect of dietary fat on intraocular pressure

No. of weeks following dietary changes	Intraocular pressure (mmHg), mean $\pm$ SD		
	Normal diet	Fat free PN	Fat supplemented PN
	14.38 $\pm$ 2.80 (28)*		
3		10.65 $\pm$ 2.60 (28)	13.92 $\pm$ 3.04 (28)
5		9.50 $\pm$ 3.20 (23)	14.18 $\pm$ 2.09 (23)
7		9.90 $\pm$ 5.09 (17)	14.38 $\pm$ 2.80 (15)

*Numbers in brackets indicate the number of patients included.

third week of fat free PN in comparison with levels measured in these same patients while on normal diet ($p=0.0001$). Supplementation of fat to the diet for three weeks was followed by an increase in ocular pressure to levels observed when these patients were on a normal diet ($p=0.001$). Comparison of IOP measurements taken when patients had been on fat free diet for three, five, and seven weeks showed they were not significantly different ($p=0.85$). The mean IOP of patients on fat free PN was lower by 3.53 ± 2.20 mmHg than the mean level measured while they were on fat supplemented diet ($p=0.0001$). Comparison of mean scleral rigidity for patients while on fat free PN and following fat supplementation was not significantly different (0.0196 ± 0.0030 and 0.0189 ± 0.0038 respectively).

The effect of dietary fat on PGE₂ plasma levels was studied in 14 of the patients and is detailed in Table 3. The results indicated that PGE₂ plasma levels were significantly lower in the patients on a completely fat free PN for three weeks than in patients on a fat supplemented PN for the same length of time ($p=0.0004$). The mean reduction in PGE₂ levels was 0.148 ± 0.0004 pg/ml ($p=0.0079$).

Discussion

EFAD occurs as a complication of fat free PN in both infants and adults and is already evident one to two weeks after initiation of this diet.¹⁻³ In patients on a normal diet linoleic acid—the only essential fatty acid in man—is elongated and desaturated to form arachidonic acid. Omission of fat causes linoleic acid deficiency with an accumulation of oleic acid, which is converted to 5.8.11 eicosatrienoic acid rather than arachidonic acid. This in the course of EFAD two processes occur that reduce PG formation: the increase in 5.8.11 eicosatrienoic acid, a potent inhibitor of PG production,⁵ and the decrease in availability of arachidonic acid, a main substrate of PG synthesis.¹

It is generally accepted that exogenous or endogenous PGs applied to the eye cause an acute rise in IOP associated with development of flare and other signs of inflammation.⁹⁻¹² However, low doses of

Table 3 Effect of dietary fat on prostaglandin E₂ (PGE₂) plasma levels

	PGE ₂ plasma levels (pg/ml), * (mean $\pm$ SD)
Fat free diet (n=14)†	0.015 $\pm$ 0.004
Fat containing diet (n=12)	0.029 $\pm$ 0.01

*Determined after patients had been on either dietary regime for three weeks. †n = the number of patients studied.

PGE₂ and PGF_{2α} topically applied to the rabbit, owl monkey, cats, or rhesus monkey eye cause a highly significant decrease in IOP distinctly different in each of the species studied.¹³⁻¹⁵ This ocular hypotension in cats and rhesus monkeys was maintained during the course of a long term topical treatment with PGE₂ and PGF_{2α} with negligible signs of irritation.¹⁶ In addition PGs are believed to act as mediators of adrenergic neurotransmission by a negative feedback mechanism in the eye and various other organs.^{19,20}

PGs have been also suggested to have a modulatory role in the ocular pharmacological effect of sympathomimetic amines in vivo based on indomethacin capability to inhibit in rabbits^{21,22} and humans²³ the hypotensive effect of topically applied epinephrine. Recently evidence for alpha-adrenergic stimulation of PGs released from rabbits and bovine irides was reported.^{24,25} PGE₂ was the major PG released.²⁴ However, it is as yet unknown how PGs exert their effect on IOP, especially in man.

In the present study the omission of fat from the diet was associated with a significant decrease in ocular pressure compared with levels noted while patients were on a normal diet. Decrease in ocular pressure was not associated with changes in scleral rigidity, though rigidity in the two groups of patients involved in our study was somewhat lower than normal (normal value for K is 0.0215).¹⁷ The reduction in IOP persisted as long as the patients were on fat deficient regimen, during a mean follow-up period of 7±1.2 weeks, and the pressure returned to normal on fat supplementation.

The development of EFAD was associated also with a significant decrease in PGE₂ plasma levels when compared with normal levels. These results are in agreement with those of Freund *et al.*,²⁶ who showed that PGE₂ metabolite levels were reduced on exclusion of dietary fat. However, lowering levels of PGE₂ metabolites in plasma does not necessarily mean a decrease in synthesis of these products. The association of IOP reduction, EFAD, and reduced plasma levels of PGE₂, though clinically interesting is not fully understood and might not necessarily indicate a casual relationship. The patients studied suffered major sickness, and therefore other factors besides EFAD might have affected changes in ocular pressure and PGE₂ levels.

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