

Letters to the Editor

Significant Hypoalbuminemia and Hypoproteinemia Associated with Myocardial Infarction in a Kuwaiti Arab Population

To the Editor: When a significant decrease in mortality from cardiovascular disease with increasing serum albumin concentrations was first reported in middle-aged British men,¹ the finding was thought to be serendipitous. However, with reports from the U.S. showing that age-adjusted relative risk for coronary heart disease (CHD) decreased with increasing concentrations of serum albumin in both white men and women,² the role of serum albumin in the etiology of CHD began to attract attention. To the best of our knowledge, the association between serum albumin and CHD has not been confirmed in other populations, neither has there been an adequate explanation for such an association if, indeed, it exists. In this retrospective study, we compared the serum concentrations of total cholesterol, triglyceride, total protein and albumin in Kuwaiti Arabs with myocardial infarction with those of healthy controls and suggested some reasons for the association between low serum albumin and myocardial infarction.

Patients and Methods

The case notes of all patients admitted to Mubarak Al Kabeer Hospital, Jabriya, Kuwait, with the diagnosis of myocardial infarction between 1992 and 1994 were examined retrospectively. Only those in which diagnosis was confirmed clinically, electrocardiographically and biochemically (elevated CK-MB) were selected for this study. We then examined the clinical biochemistry reports of those who were recorded to be Kuwaitis and compared their serum concentrations of total cholesterol, triglyceride, total protein and albumin with those of healthy controls. Simple descriptive statistics (mean, standard deviation) were used to analyze results from patients and controls. For comparing the various parameters studied among groups, analysis of variance (ANOVA) with age as a covariate was used. These analyses were carried out using the statistical package SPSS version 6.

Results

Table 1 shows that serum triglyceride concentration was significantly higher in myocardial infarction than in controls. On the other hand, there was no significant difference in total serum cholesterol between cases and controls. Total serum protein and albumin were significantly lower in MI than in controls. In order to

determine if there was any association between serum albumin and myocardial infarction, we calculated the odds ratio by taking a serum albumin level of 45 g/L as reference. Based on the calculated odds ratio (Table 2), a level of serum albumin below 40 g/L showed a significantly higher ($P < 0.0001$) risk (OR=16.57, CI=7.1-38.7) for myocardial infarction than a serum albumin concentration of 45 g and above, suggesting an inverse relationship between serum albumin concentration and risk for myocardial infarction.

Discussion

There are two important findings in this report that deserve comment: the significant hypertriglyceridemia and the hypoalbuminemia associated with myocardial infarction in Kuwaiti Arabs.

For quite a long time, the association between serum triglyceride and CHD remained unclear. In a large number of both case control and cross-sectional studies, an association between increased serum triglyceride and myocardial infarction was reported, but only in three of the studies³⁻⁵ did the association remain significant after controlling for other confounding factors. Recently, Bainton et al.⁶ reported that triglyceride was an independent risk factor for CHD. In addition, the PROCAM study⁷ showed that serum triglyceride was an independent risk factor for CHD. Our finding that Kuwaiti Arabs with myocardial infarction had significantly higher triglyceride concentration than healthy controls supports an association between serum triglyceride and MI. Epidemiological, clinical and experimental studies suggest that hypertriglyceridemia predisposes an individual to thrombosis by increasing factor VII coagulant activity.⁸ It is therefore suggested that hypertriglyceridemia may be an important risk factor for CHD in Kuwaiti Arabs.

Another important finding in this study was the association between hypoalbuminemia and CHD, an observation first reported in Britain by Philips et al.¹ and later confirmed in the U.S. by Gillum and Makuc.² There have been no detailed explanations for this association. Philips et al.¹ claimed that the association could not be explained by any correlation between serum albumin and factors known to be related to mortality, and that they could not rule out the fact that their observation might be a chance finding. Gillum and Makuc,² on the other hand, claimed that the lack of a plausible mechanism for an effect of serum albumin on the incidence of CHD suggests that it may be an indicator of some factor influencing some stage of atherosclerotic process from initiating lesions to precipitating events. They further suggested that effects of albumin concentration on blood viscosity and free fatty acid transport might be considered. We propose that hypoalbuminemia in MI may be due to a combination of

microalbuminuria,⁹ increased loss of albumin into extravascular spaces,¹⁰ and increased degradation of plasma proteins by free oxygen radicals.¹¹

Since protein sulfurhydryls serve as sacrificial antioxidants, preventing plasma lipid peroxidation as well as being targets for oxidative damage,¹² we propose that hypoalbuminemia leads to a reduction in the oxidant-scavenging capacity of plasma proteins and this, in turn, induces myocardial muscle damage by free oxygen radicals.

In conclusion, although the number of cases of MI in this study was small, and a larger number would need to be investigated, our study suggests that there is an association between hypoalbuminemia and myocardial infarction in Kuwaiti Arabs.

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Vitiligo: A Study of 112 Cases

To the Editor: Vitiligo is an inherited or acquired non-infective disease, characterized by well-defined, milky-white, depigmented macules associated with or without systemic features. The word "vitiligo" has probably evolved, in Arabic literature, from the word "buhak," often used locally as a synonym for a similar word, "baras," which means "leprosy," an infective, chronic, cutaneous disease, commonly manifested by hypopigmented skin. However, Leider & Rosenblum (1968)¹ defined it as a "blemish," a term that further casts a stigma on patients with vitiligo, creating traumatic psychosocial public relationships for these patients.²

However, even though certain hypotheses have been put forward, the etiopathogenesis of this disease is unknown, although its pathology, including the electron microscopic features, has been described.³

This prospective study looked at the clinical presentation of vitiligo among the dermatology patients attending King Fahad Hospital, Al Baha, Saudi Arabia, from November 1, 1990 to October 31, 1991. All subjects in this study were consulted for family and past history of diabetes mellitus, thyroid and ocular disease, anemia, duration of the disease, precipitating factors, consanguineous marriages, occupation, gastrointestinal and neurological complaints. Each patient was then clinically examined, detailing the site, type of vitiligo and other diseases.

Laboratory investigations for each patient included fasting blood sugar, VDRL, urea, creatinine, liver function tests (LFT), CBC, hepatitis profile (where indicated), thyroid function tests, antinuclear factor (ANF), thyroid antibodies (TA), DNA, lupus erythematosus cell test (LE), gastric (parietal) antibodies (GA), mitochondrial antibodies (MA) and detailed eye examination by an ophthalmologist.

Subsequently, each patient was treated with twice weekly heliotherapy, augmented by oral or topical 8-methoxypsoralen, vitamin B complex and nocturnal topical, with or without systemic corticosteroids. Individuals with abnormal LFTs and cardiomyopathy were only given topical psoralen treatments. The treatment was adjudged "better" or "no change" by presence or absence of repigmentation of the area or reduction in size of the vitiliginous skin. One of the patients ascribed previous minimal therapeutic improvement to an Arabic medicinal herb, "Atmanta," which was chemically analyzed by gas-liquid chromatography and mass spectrophotometry. The

TABLE 1. *Clinico-epidemiological pattern of vitiligo.*

	Age 0-19		Age 20-39		Age 40-59		Age ≥60		Total	
	M	F	M	F	M	F	M	F	M	F
Family history										
Diabetes	9	12	3	4	2	8	2	-	16	24
Vitiligo	4	5	3	2	-	4	1	1	8	12
Thyroid	-	2	-	1	-	3	-	-	-	6
Site										
Legs	9	9	8	8	5	9	6	-	28	26
Palms	-	3	3	1	-	4	-	-	3	8
Eyelids	3	15	-	3	-	-	-	-	3	18
Mucus membranes	-	1	2	-	-	-	-	-	2	1
Multiple sites	1	2	1	-	1	5	2	2	5	9
Treatment										
Prednisone	7	22	10	8	3	14	3	-	23	44
Steroids	9	30	13	11	4	16	6	2	32	59
Vit. B12	9	24	7	9	3	15	5	2	24	50
PUVA	8	28	12	11	4	15	4	2	28	56
Condition										
Improved	10	26	11	11	3	12	4	2	28	51
No change	2	6	4	1	2	4	2	-	10	11
No report	1	2	1	1	2	2	2	1	6	6
Total patients	13	34	8	7	3	5	8	3	44	68

pharmacological action of the main constituent, xanthotoxin, was deduced from Martindale's *Pharmacopoeia*.¹⁴ Out of 4025 new dermatology patients seen, 112 had vitiligo: 44 males (39%) and 68 females (61%), aged 34±19 years and 27±18 years respectively. There were 108 Al Baha Saudis (96%), 41 males (38%), 67 females (62%) and four non-Saudis (two Indians, two Pakistanis: 3M, 1F). There was a positive family history of diabetes mellitus, vitiligo and thyroid diseases in 40 (35%), 20 (18%), and six (5%) patients respectively. The disease was congenital in three patients (2.7%). The associated diseases observed were: halo nevus (three patients, 2.7%), conjunctivitis (four patients, but no detailed eye examination was done, e.g., for uveitis), peptic ulcer or dyspepsia (three patients, 2.7%), trauma (two patients, 1.8%), thyrotoxicosis (two patients, 1.9%), chronic lymphatic leukemia (one patient) and cardiomyopathy (in four patients, 3.5%), diabetes mellitus in seven patients (six were non-insulin dependent). It was not ascertained whether the diabetic patients were initially on insulin and were later converted to oral hypoglycemic agents.

The duration of the disease was variable: 1-5 years (90 patients, 81%), 6-10 years (12 patients, 11%), over 10 years (one patient, 1%) and nine patients (7%) were not sure. Our results show that the disease was common on the lower limbs (48%), eyelids (19%), palmar (10%), mucous membranes (lips) (3%), while 28 (25%) of the

patients had serological autoantibodies: ANF (7%), TA (6%), DNA (5%), AM (2%).

The major active ingredient of "Atmanta" was xanthotoxin, an analogue of psoralen. There were two minor insignificant components present in the herb (isopimpinellin and 7-hydroxyfurobenzopyrone).

Seventy-nine (70%) of the patients improved on treatment, but 21 (19%) were resistant (more of the palmar vitiligo patients), while 12 patients (11%) defaulted. Side effects of treatment observed during the study were: erythema, pruritus, bullae, burns, hyperpigmentation and hypertrichosis.

It was observed that 2.7% of the population had vitiligo. This is consistent with results of previous investigations by Jorrallah et al., in a retrospective study from Riyadh, Saudi Arabia, who reported a similar incidence of 2.3%.⁴ However, the pattern in sub-Saharan Nigeria was different.^{5,6}

The present study indicates that more females are affected by vitiligo than men, in contrast to George and McBurney, who noticed a higher incidence in men.^{5,7} The positive family history of vitiligo in some patients indicates a genetic predisposition in these individuals. The presence of vitiligo in monozygous twins and the occurrence of HLA-DR4-associated vitiligo among black Americans lends support to this theory.^{8,9} Furthermore, some organ-specific autoantibodies (TA, GA, MA) were more common in females and patients with palmar, mucous membrane or eyelid vitiligo. Such correlation may be used as a diagnostic or prognostic marker in the management of this disease.

Although an autoimmune hypothesis had been advocated for vitiligo, most of the claims were indirect. Out of the 13 patients described in the treatise on "Addison's disease," two patients had vitiligo,⁸ while Howitz and Schiwatz¹⁰ reported association of vitiligo and pernicious anemia. However, Hertz et al., more convincingly, reported autoantibodies to melanin-producing cells in vitiligo.¹² Even though melanocyte autoantibodies were not measured in our study, the presence of circulating autoantibodies in the sera of Al Baha vitiligo patients probably indicates or supports the autoimmune theory of vitiligo. Furthermore, the strong family history of autoimmune thyroid disease and diabetes mellitus lends further support to this theory.

Our study shows that 5% of the patients had associated diabetes mellitus, although 90% of these had NIDDM. It will be expected that IDDM will be more common than NIDDM, since both diabetes mellitus and vitiligo are organ-specific autoimmune diseases.¹³ The result also revealed that 4% of the patients had conjunctivitis.⁸ Unfortunately, these patients were not followed up for any evidence of uveitis, since the latter had been associated with vitiligo.⁸

Seventy percent of the study group responded positively to treatment, while those with autoimmune palmar vitiligo were resistant. The Saudi medicinal herb "Atmanta" was found to contain a psoralen, which is the active chemical agent used in activating vitiliginous or psoriatic skin to ultraviolet radiation. Therefore, it was not surprising that the patient who used this unquantifiable medicinal herb responded slightly. Such a local medicinal plant may be used to manufacture psoralen drugs by the local pharmaceutical industries through collaboration between pharmacists, scientists, botanists and physician dermatologists. Although some cases of localized vitiligo had been treated successfully with surgical transplantation of autologous normal melanocyte skin,¹⁵ immunomodulation with corticosteroids, PUVA and neurotonics constitutes the mainstay of vitiligo treatment. There is a need for a cheap therapeutic regime in the management of this common chronic disease in this environment.

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Is Tazocin™ (piperacillin/tazobactam) effective against non β -lactamase producers?

I have read, with interest, the article entitled "Antibacterial activity of Tazocin™ (piperacillin/ tazobactam) against 1296 clinical isolates from a tertiary care center" by Qadri et al., which appeared in the *Annals of Saudi Medicine*.¹ The effect of tazobactam is to inhibit a wide spectrum of β -lactamases and the authors have rightly mentioned that they have insignificant antibacterial activity. When piperacillin or any other antibiotic is combined with this drug, it serves only to help against organisms which have developed their resistance because of β -lactamase production. The authors have mentioned that most of the methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococci* and *Pseudomonas aeruginosa* were resistant to piperacillin but sensitive to tazocin. However, the resistance of *Enterococci*, MRSA, and *Pseudomonas aeruginosa* to β -lactamase drugs is not mainly due to the production of β -lactamase, but the result of many other factors and mechanisms. In fact, β -lactamase has been described only in a small number of these isolates² and hence it would appear inappropriate to recommend piperacillin/tazobactam even if they appear susceptible on the sensitivity plate, the exception being when resistance due to β -lactamase production has been confirmed. If the organisms under consideration are demonstrated to produce β -lactamase then we could assume that these would be sensitive to piperacillin/tazobactam.

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Reply

To the Editor: With reference to Dr. Butt's letter regarding our article in the *Annals* (1996;16:377-80), we would like to emphasize that piperacillin, a ureidopenicillin, has greater *in-vitro* activity against *Enterococci* and other gram-positive bacteria than amino- or carboxy-penicillins. In our paper, we stated that tazobactam has a wide

spectrum of affinity that includes classes I, II, IV and V β -lactamases. The abstract of the paper clearly states that the combination of tazobactam with piperacillin was effective against piperacillin-resistant organisms, including *S. aureus* and *Enterococci*. We concur with Dr. Butt that irrespective of the *in-vitro* activity, the combination could and should only be used against β -lactamase producers, because tazobactam is nothing but a penicillanic acid sulfone derivative which acts as a β -lactamase inhibitor and binds to bacterial PBP 1 and PBP 2. We presented the *in-vitro* activity data which is consistent with other investigators' findings.¹⁻³ We are certain that Dr. Butt knows that many organisms appear susceptible to certain antimicrobials *in-vitro* without any clinical efficacy. The best examples are the many MRSA which appear susceptible to first-generation cephalosporins, however, microbiologists as well as clinicians know that these drugs are contra-indicative. We feel that Dr. Butt mistook our *in-vitro* data to mean that we were recommending the use of combination in clinical practice for MRSA, etc. At no point in the article did we say anything about the clinical efficacy of piperacillin/tazobactam against such organisms.

Our discussion was centered around the potentiation of piperacillin by the ability of tazobactam to inhibit both plasmid as well as chromosomally mediated β -lactamases (see paragraphs 1 and 2 of 'Discussion').

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