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A Case-Control Study of Dietary Intake of Renal Stone Patients

I. Preliminary Analysis

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Summary. The average daily dietary intake of 88 idiopathic renal stone cases and 88 age and sex matched controls was assessed by history using a standardised questionnaire. Statistical analysis was undertaken on the whole group and on male and female subgroups, to establish if there were any significant differences between cases and controls. There were statistically significant differences in dietary intake between the whole group, the female cases and the control group. Male cases showed only a significantly lower intake of thiamine compared to controls. There was little difference between cases and controls intake of iron or multivitamin supplements but vitamin C supplements (> 1 g/day) were taken more than twice as frequently by cases than controls. These results suggest that control dietary studies of renal stone patients without regard to their sex may conceal many differences in dietary intake between cases and controls.

Key words: Renal stones, Control study, Dietary intake, Dietary supplements.

Introduction

Renal stone disease is a painful and potentially dangerous condition and is one of the most frequent causes of acute surgical admission [37]. In Ireland, an average of 2.4/10,000 of the population are admitted to hospital annually for renal stones [2] and many more are treated on an outpatient basis.

A large number of dietary factors have been associated with renal stone formation. Epidemiological studies indicate an association between a high animal protein intake and a high stone incidence [4, 40, 41]. The incidence of stones in vegetarians is reported to be only 40–60% of that predicted for an age, sex and social class matched non-vegetarian group [42], the difference being attributed to the lower intake of animal protein in the vegetarian group. A high stone incidence has also been associated with a high sugar, fat and refined carbohydrate intake [4], with a low dietary fibre intake [4, 19, 41] and with a low phytic acid intake [33]. A negative correlation has also been shown between green vegetable and fruit consumption and the incidence of renal stones disease [43]. There is little evidence to show that renal stone incidence is increased in hard water areas [2, 16] although one group observed that 24% of a sample of 308 renal stone patients drank hard water for more than one week prior to diagnosis [18]. An increased incidence of renal stones was reported to coincide with soft water areas [12, 43] although Wales and SE England have a low incidence despite being soft water areas [43].

Despite the differences in dietary intake found between populations in areas of high and low renal stone incidence, no major control studies have been reported that directly assessed the dietary intake of renal stone patients in relation to their urine biochemistry and stone composition. A pilot study of dietary intake of renal stone cases was conducted in this unit in 1978 [20] but cases were surveyed regardless of underlying aetiological factors present. That study did not reveal significant differences in dietary intake between cases and controls. The intake of dietary fibre and the % of energy provided by carbohydrate were consistently lower and the % of energy provided by fat was consistently higher in the case group.

In October 1980, this case-control study was undertaken to compare the usual dietary intake of renal stone patients with that of the normal stone free population both as a total group and as sub-groups established on the criteria of sex, urinalysis and stone analysis. Eighty-eight cases and 88 suitable matched controls were interviewed over a period of 15 months. The nutrient content of the diets of case and control groups was analysed and compared using standard statistical methods. This paper examines the differences

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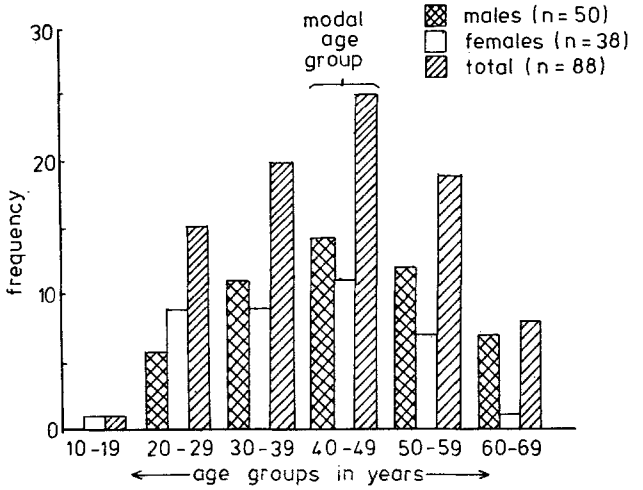

Fig. 1. Distribution of renal stone cases according to age and sex

between the total group, male and female subgroups and their matched controls regardless of urine biochemistry or stone composition.

Patients and Methods

The study sample consisted of all suitable patients and outpatients with renal stone disease attended by the genitourological unit of a Dublin hospital during the period of study. Renal stones were diagnosed by colic and/or haematuria followed by radiological examination or by the passage or surgical removal of stone. The following inclusion criteria were applied; that the subject (a) was between the ages of 18 and 70 years, (b) had had no dietary instruction and had made no dietary changes since the diagnosis of renal stones, (c) had a consistent dietary pattern, (d) had no history or evidence or any disease or abnormalities which could influence the formation of renal stones including presence of bladder stones, (e) was intelligible and willing to co-operate in the study, (f) provided at least one 24 hour urine collection for biochemical analysis or one stone for analysis.

Age of cases ranged from 19–66 years with a mean age of 42.7 ∓ 2.56 years. The sample of 50 men and 38 women had a ratio of four males to three females. Eighty-one cases were first time stone formers (45 men and 36 women) and the remainder were recurrent stone formers. There was a greater proportion of cases from urban than rural areas with 72% urban and 28% rural dwellers in the total sample. Figure 1 shows the distribution of renal stones cases according to age and sex.

The control group included patients of the genito-urological unit who had no history or evidence of urinary tract stones, who were under observation or treatment for conditions which did not involve dietary problems or treatment and who considered themselves to be on their normal diet. Having satisfied these requirements, each control was matched with a case for age, sex and area of residence. Controls were on average older than cases and their ages ranged from 20-67 years with a mean age of 48.3 ∓ 3.37 years.

Subjects were divided into urban and rural dwellers, as the diets of these two groups were considered likely to differ. These subgroups were formed for the purpose of matching with controls only and subjects were not sub-divided according to area of residence for purpose of analysis.

Dietary Assessment Methodology

Dietary information was collected by interview and included a dietary history modified from the method of Burke [10] of an average weekly intake using a standardised questionnaire. The average daily intake derived from weekly totals was then estimated and expressed in terms of nutrient per individual (whole body mass) and nutrient intake per kilogram of actual body weight or in the case of overweight subjects per kilogram of maximum ideal body weight calculated from weights and heights using standardised tables [32]. This "estimated fat free mass" (EFFM) was used in the calculations of results as body fat is not known to play an active role in renal stone formation and therefore overweight subjects would have distorted the results in relation to the metabolic effect of their nutrient intakes, had excess fat been included. A frequency chart was also included. This incorporated a list of commonly eaten foods and high risk foods (i.e. foods containing large amounts of purine, oxalate, calcium and vitamin D) and served as a cross check to assist the subject in remembering his usual dietary intake and the occasional intake of significant amounts of high risk foods.

Data were also collected on the intake of dietary supplements, laxatives and antacids and on smoking habits and occupational activities of the participants. Results of intake of dietary supplements and occupations of subjects are presented in this report while the remainder, laxitive and antacid intake and smoking habits will be reported in further communications.

Dietary Analysis

The energy and nutrient content of 969 foods was stored on file for computer analysis of the diets. Food composition data was taken from six sources; for macronutrients, vitamins, minerals and phytic acid [35], purine [15, 30], oxalate values [23, 26, 49] and dietary fibre [35, 46].

Each diet was analysed for the content of 30 nutrients; energy, total protein, animal protein, fat, carbohydrate, cellulose, non-cellulose polysaccharide, lignin, total dietary fibre, vitamin A, retinol, carotene, thiamine, niacin, riboflavin, pantothenic acid, pyridoxine, total folic acid, vitamin B12, vitamin C, calcium, phosphorus, iron, magnesium, potassium, copper, tryptophan, phytic acid, purine nitrogen and oxalate. In the determination of dietary intakes, it was beyond the scope of this study to consider the bioavailability of nutrients, therefore only the chemically analysed nutrient content of the diet was taken into account. Sodium and vitamin D intake were not assessed, the former, because of the difficulty in measuring salt in cooking and at table and the latter, because dietary vitamin D intake would only provide an incomplete estimation of vitamin D nutritional status without an assessment of 25-hydroxy-vitamin D3 derived from sunlight exposure.

Statistical Analysis

Statistical analysis of the dietary intake of cases and controls was undertaken to establish if there was any significant difference in intake between the two groups with respect to each of the 27 nutrients and three dietary risk factors investigated. This analysis included the calculation of the mean, the standard error of the mean and the application of the paired-sample t-test for each nutrient under investigation; it was conducted on the total group of 88 pairs and on the male and female subgroups.

Results

The average dietary intake, the standard error of the mean of each nutrient/risk factor and paired t-tests for differences

Table 1. Differences in the average daily intake of nutrients for cases and matched controls on whole body and estimated fat free mass basis

Nutrients (Units)	Intake per whole body mass				Intake per kg estimated fat free mass			
	Cases (n = 88)	Controls (n = 88)	mean diff.	P	Cases (n = 88)	Controls (n = 88)	mean diff.	P
	$\bar{x}$ $2SE_{\bar{x}}$	$\bar{x}$ $2SE_{\bar{x}}$			$\bar{x}$ $2SE_{\bar{x}}$	$\bar{x}$ $2SE_{\bar{x}}$		
Total protein (g)	108.80 ± 6.83	104.03 ± 2.58	4.75	NS	1.687 ± 0.119	1.632 ± 0.148	0.005	NS
Animal protein (g)	76.21 ± 5.44	72.30 ± 5.46	3.91	NS	1.179 ± 0.088	1.109 ± 0.084	0.070	NS
Fat (g)	141.72 ± 11.81	127.42 ± 11.30	14.30	NS[a]	2.173 ± 0.173	2.014 ± 0.220	0.159	NS
Purine (mg)	160.41 ± 16.75	138.13 ± 11.81	22.28	< 0.05	2.492 ± 0.299	2.132 ± 0.190	0.360	< 0.05
Vitamin A (mg)[b]	2.76 ± 0.60	2.14 ± 0.31	0.62	NS[a]	0.044 ± 0.010	0.032 ± 0.005	0.012	< 0.05
Retinol (mg)[b]	2.40 ± 0.63	1.51 ± 0.30	0.89	< 0.02	0.037 ± 0.010	0.024 ± 0.005	0.013	< 0.02
Carotene (mg)[b]	3.20 ± 0.38	3.80 ± 0.53	−0.06	NS[a]	0.049 ± 0.006	0.060 ± 0.009	−0.011	< 0.05
Thiamine (mg)	1.66 ± 0.12	1.87 ± 0.21	−0.21	NS[a]	0.026 ± 0.002	0.030 ± 0.005	−0.004	NS[a]
Vitamin B12 (μg)	13.45 ± 2.83	9.94 ± 1.38	3.50	< 0.02	0.211 ± 0.045	0.162 ± 0.024	0.049	< 0.05
Copper (mg)	2.83 ± 0.37	2.34 ± 0.24	0.49	< 0.05	0.044 ± 0.006	0.037 ± 0.004	0.007	< 0.05

NS = not significant
[a] < 0.10 level of probability
[b] normally expressed in μg

Table 2. Differences in the average daily intake of nutrients for male cases and matched controls on whole body and estimated fat free mass basis

Nutrients (Units)	Intake per whole body mass				Intake per kg estimated fat free mass			
	Cases (n = 50)	Controls (n = 50)	mean diff.	P	Cases (n = 50)	Controls (n = 50)	mean diff.	P
	$\bar{x}$ $2SE_{\bar{x}}$	$\bar{x}$ $2SE_{\bar{x}}$			$\bar{x}$ $2SE_{\bar{x}}$	$\bar{x}$ $2SE_{\bar{x}}$		
Thiamine (mg)	1.70 ± 0.17	2.11 ± 0.32	−0.41	< 0.05	0.025 ± 0.003	0.034 ± 0.007	−0.009	< 0.05
Non-cellulose polysaccharide (g)	15.94 ± 1.72	18.47 ± 2.44	−2.53	NS	0.222 ± 0.026	0.262 ± 0.034	−0.040	NS[a]
Phytate (mg)	154.72 ± 37.25	200.61 ± 41.89	−45.89	NS[a]	2.131 ± 0.512	2.792 ± 0.574	−0.611	NS[a]

[a] < 0.10 level of probability

Table 3. Differences in the average daily intake of nutrients for female cases and matched controls on whole body and estimated fat free mass basis

Nutrients (Units)	Intake per whole body mass				Intake per kg estimated fat free mass			
	Cases (n = 38)	Controls (n = 38)	mean diff.	P	Cases (n = 38)	Controls (n = 38)	mean diff.	P
	$\bar{x}$ $2SE_{\bar{x}}$	$\bar{x}$ $2SE_{\bar{x}}$			$\bar{x}$ $2SE_{\bar{x}}$	$\bar{x}$ $2SE_{\bar{x}}$		
Energy (MJ)	11.61 ± 1.08	9.84 ± 1.11	1.77	< 0.02	0.186 ± 0.017	0.159 ± 0.024	0.027	< 0.05
Total protein (g)	101.20 ± 7.92	87.61 ± 8.05	13.59	< 0.025	1.631 ± 0.146	1.411 ± 0.182	0.220	< 0.05
Animal protein (g)	70.91 ± 6.39	63.23 ± 7.20	7.68	NS	1.294 ± 0.136	1.102 ± 0.136	0.192	< 0.05
Fat (g)	135.23 ± 15.51	111.81 ± 67.91	23.42	< 0.025	2.162 ± 0.240	1.819 ± 0.337	0.343	< 0.05
Carbohydrate (g)	298.14 ± 31.08	258.11 ± 30.69	40.03	NS[a]	4.793 ± 0.513	4.168 ± 0.303	0.625	NS[a]
Purine (mg)	152.11 ± 29.59	119.63 ± 15.28	32.48	NS[a]	2.773 ± 0.594	2.103 ± 0.292	0.670	< 0.05
Vitamin A (mg)[b]	3.02 ± 0.95	2.02 ± 0.48	1.00	NS[a]	0.054 ± 0.017	0.036 ± 0.008	0.018	< 0.05
Riboflavin (mg)	2.59 ± 0.36	2.10 ± 0.27	0.49	< 0.05	0.042 ± 0.006	0.034 ± 0.006	0.008	NS[a]
Niacin (mg)	21.23 ± 2.57	17.46 ± 1.57	3.77	< 0.025	0.341 ± 0.042	0.279 ± 0.032	0.062	< 0.05
Pantothenic acid (mg)	5.96 ± 0.67	4.98 ± 0.56	0.98	< 0.05	0.096 ± 0.011	0.081 ± 0.012	0.015	NS
Retinol (mg)[b]	2.68 ± 0.54	1.32 ± 0.40	1.36	< 0.025	0.042 ± 0.017	0.022 ± 0.007	0.020	< 0.05
Vitamin B12 (μg)	13.85 ± 4.45	8.44 ± 1.96	5.41	< 0.025	0.220 ± 0.068	0.138 ± 0.036	0.082	< 0.05
Cellulose (g)	5.35 ± 0.53	4.72 ± 0.47	0.63	NS	0.097 ± 0.010	0.083 ± 0.009	0.014	< 0.05
Tryptophan (g)	1.29 ± 0.10	1.11 ± 0.11	0.18	< 0.02	0.021 ± 0.002	0.018 ± 0.003	0.003	< 0.05
Iron (mg)	14.64 ± 1.72	11.83 ± 0.98	2.81	< 0.02	0.231 ± 0.027	0.193 ± 0.022	0.038	< 0.02
Copper (mg)	2.80 ± 0.60	1.88 ± 0.24	0.92	< 0.01	0.044 ± 0.009	0.030 ± 0.005	0.014	< 0.01
Potassium (g)[c]	3.84 ± 0.33	3.33 ± 0.33	0.51	NS[a]	0.063 ± 0.007	0.054 ± 0.008	0.009	NS[a]

[a] < 0.10 level of probability
[b] normally expressed in μg
[c] normally expressed in mg

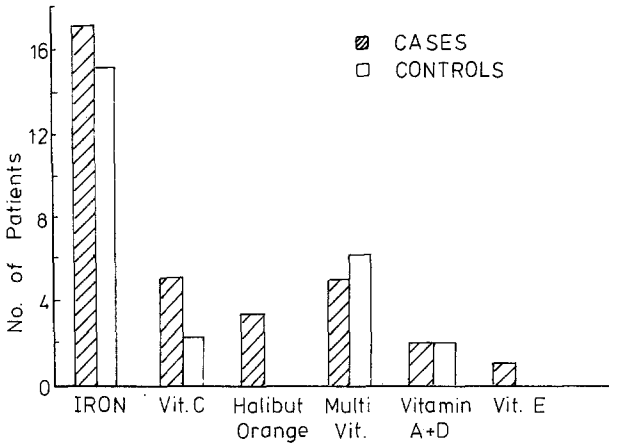

Fig. 2. Comparison of iron and vitamin supplement intake of cases and controls over the two year period preceding interview

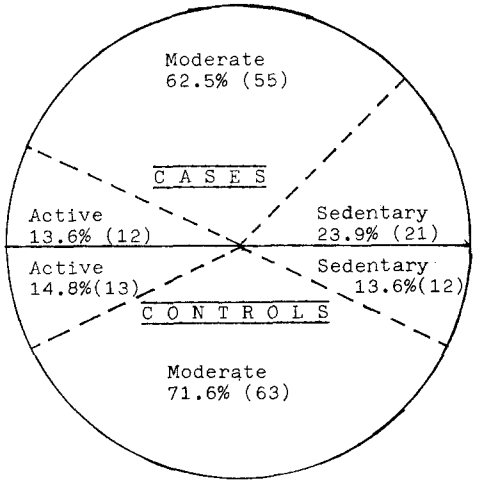

Fig. 3. Comparison of occupational activity ratings of cases and controls

between the correlated sample pairs are shown in Tables 1, 2 and 3 for the total group, male and female subgroups respectively. As this is a study of differences in dietary intake rather than absolute intake of two groups, only those that show a difference of at least 0.10 level of probability between cases and controls are presented, although differences of >0.05 level of probabilities are not considered to be significant. In all the following tables of dietary intake results, a negative mean difference indicates that the case group had a lower intake of the nutrient than the control group. Results expressed as mean nutrient intake per individual (WBM) are presented only to facilitate comparison with recommended dietary allowances and other dietary studies of renal stone patients with results presented in this way. Discussion will be centred mainly on the results expressed per kilogram "estimated fat free mass" (EFFM).

Table 1 shows that the total case group had a significantly higher intake of purine, vitamin A, vitamin B12, copper ($P < 0.05$) and retinol ($P < 0.02$) and a significantly lower intake of carotene ($P < 0.05$) than the control group when results were expressed per kg. EFFM per day. Table 2 shows that male cases had only one significant difference in dietary intake compared to controls, that of a lower thiamine intake ($P < 0.05$). Table 3 shows that female cases had many differences in dietary intake compared to controls with 13 nutrients showing a significant difference between the two groups, copper ($P < 0.01$) and iron ($P < 0.02$) showing the greatest differences.

Figure 2 compares the regular iron and vitamin supplement intakes of cases and controls. There was little difference found in the intake of iron, multivitamins or vitamin A, D and E supplements but the frequency of consumption of vitamin C supplements (< 1 g/day) by the case group was more than twice that of controls. Halibut orange tablets (containing vitamins A, D and C) were only taken regularly by cases.

Figure 3 compares the occupational activities of cases and controls. Almost twice the number of cases ($n = 21$) had sedentary occupations compared to controls ($n = 12$) and there is little difference between cases and controls in the moderate and active occupations.

Discussion and Conclusions

In order that a case-control study may yield useful information, the study sample must be representative of the total population one wishes to study. The urban/rural ratio and age and sex distribution of our sample compares well with that of renal stone admission rates to Irish hospitals for the years 1971–1974 [2]. That report showed that 68% of patients were urban dwellers compared to our 72% urban sample and had a male to female ratio of 1 : 0.66 compared to our 1 : 0.76. The male modal age group (40–49 years) was the same as ours but those of females and both sexes together (a modal age group 30–39 years) differed with Fig. 1. Assuming that the Irish data [2] reflect that of the total renal stone population of Ireland, then our sample would appear to be fairly representative of Irish renal stone patients in terms of urban/rural residence, age and sex distribution.

The total group was studied regardless of stone type or underlying aetiological factors; the only common factor was the presence of calcium in their stone, i.e. it was radiopaque or was surgically removed with subsequent analysis revealing the presence of calcium. Despite the probable mixed cause of renal stone formation in this group, there were six significant differences found between the cases and controls (Table 1).

Purine is known to influence the formation of both calcium [39] and uric acid stones [34]. A high purine intake increases production and excretion of uric acid [13, 21] which in turn decreases the effect of glycosaminoglycans, inhibitors of calcium oxalate crystal growth [36]. Hyperuricosuria can cause supersaturation and formation of monosodium urate and uric acid crystals and the spontaneous

nucleation of calcium oxalate, by providing preformed nuclei upon which calcium oxalate can crystallise [14, 34]. Increased purine intake also increases oxalate excretion, probably by increasing endogenous synthesis of oxalate [50] which in turn increases the risk of calcium stone formation [39]. Foods high in purine often have a low pH ash content and therefore not only increase uric acid excretion but also acidify urine which facilitates the precipitation of uric acid crystals [45]. The higher purine intake in the case group is probably predominately from organ meats rather than from meat, as the total protein and animal protein intakes did not differ significantly between the two groups (Table 1). The significantly greater intake of retinol, copper and vitamin B12 in the case group would support this interpretation as organ meats are an excellent source of these nutrients. Although purine intake was found to be a major risk factor of calcium stone disease [39], no major epidemiological studies have examined the intake of purine in relation to renal stone incidence. A positive correlation has been reported with a probable increase in purine intake accompanying it [40, 41] but others have reported a negative correlation between meat intake and renal stone incidence [43].

The higher intake of vitamin A by the case group supports the observation that vitamin A intake is related to renal stone formation [5]. Toxic quantities of vitamin A have been associated with hypercalciuria, medullary nephrocalcinosis and renal stone disease [7]. However, the mean intake of vitamin A of our cases (2,763 μg/day) could hardly be described as a toxic dose. When vitamin A activity is divided into retinol and carotene intake, cases have a significantly higher intake of retinol and a significantly lower intake of carotene than controls. As neither of these nutrients have previously been associated with renal stone formation, this finding is probably not relevant but merely a consequence of the type of food as opposed to the nutrient intake of the two groups.

The results presented in Table I show that there were more differences in dietary intake between cases and controls and those found were more significant than in that of our pilot study [20]. This can probably be explained by the improvement in our study design; a larger case sample, more detailed criteria for case selection, results analysed as nutrient intake per kilogram of estimated fat free mass rather than per kilogram of actual body weight and an improved and extended nutrient data base.

The male case group (Table 2) showed only one significant difference in dietary intake from the control group, that of a lower intake of thiamine. Thiamine deficiency has been shown to cause an increase in oxalate excretion in rats [47] but no reports of human cases have been published to our knowledge. Increases in glyoxalate blood levels have been reported in two patients with thiamine deficiency [9]. Glyoxalate is an immediate precursor of oxalate and about 40–50% of urinary oxalate is formed as a result of its metabolism [31]. Using the British recommended dietary allowances (1979) of 0.4 mg thiamine per 4.2 MJ per day for adult man, only four male cases (8%) had thiamine intakes below this level (two of whom had hyperoxalauria) but whether this reflected a clinical deficiency could not be determined without further studies on the particular individuals.

Many of the nutrient intake differences found between the female case and control groups (Table 3) have previously been associated with renal stone formation. This association has already been described for high vitamin A intake [5, 7] and high purine intake [34, 39]. A high total protein and animal protein intake has been related to the level and pattern of stone incidence in a population in the context of the level of economic development [3, 38, 40] and has also been shown to increase urinary calcium excretion in normal subjects [1, 8, 11, 29] and in renal stone patients [28, 38]. A high fat intake has been identified with renal stone formation [25]; fatty acids form insoluble soaps with calcium, thereby reducing its absorption and consequently increasing the absorption of oxalate. Fat is also a vehicle for vitamins A and D, both associated with renal stone formation. The ingestion of tryptophan, an oxalate precursor could result in an increased urinary oxalate excretion.

Iron, copper, vitamin B12, retinol, pantothenic acid, niacin and riboflavin have not been identified as contributors to renal stone formation and probably only indicate which types of foods were taken in larger amounts by cases than controls. The common rich source of all these nutrients is liver and, with the exception of retinol, red meat. Both are excellent sources of copper and iron, the nutrients showing the greatest difference between the two groups.

Cellulose intake (a component of dietary fibre) was also significantly greater in the female cases than controls, although there was no significant difference in the total dietary fibre, non-cellulose polysaccharide or lignin intake. This can be explained by the fact that the percentage of cellulose in wholegrain cereals is not reduced significantly by refining, unlike total dietary fibre. A high cellulose intake is not associated with renal stone formation and the greater intake found in the female case group may best be interpreted by the overall greater nutrient density of their diets.

The large number of significant differences found between the dietary intake of female cases and controls and the relative absence of significant differences found between the male cases and controls merits further comment. The latter findings would suggest that the normal (stone-free) Irish male population has a nutrient intake similar to the male renal stone population. Consequently, the normal male population may be at greater risk of forming a stone in the future, due to the nature of their diet, than the normal female population. This could, in part account for the higher admission rates for stone disease found in the Irish male population [2].

The difference in vitamin C supplement intake found between cases and controls (Fig. 2) is interesting, especially since large doses of vitamin C (>1 g/day) have been impli-

cated in causing hyperoxalauria in normal stone free subjects [6, 22, 24, 44] although others have not found this to be so [17, 27, 48]. In our study, three of the five cases taking at least lg. vitamin C per day had hyperoxalauria. This is a surprising find considering the small number of cases and relatively low doses involved and strenthens the argument that some individuals are more than usually efficient at converting vitamin C to oxalate [6].

The greater proportion of cases in sedentary occupations compared to controls (Fig. 3), supports the observation that renal stones are more common in those with sedentary rather than physically active occupations [37].

Due to the large numbers of nutrients studies in the diets of cases and controls, it was only possible to analyse the nutrient intakes individually although the synergistic effect of nutrients in the diet is probably more important in determining the biological effects arising from metabolic interdependence. It is hoped to analyse our data further taking this fact into account and this will hopefully confirm many of our present observations. The sub-grouping of cases according to sex established a totally different pattern of dietary intake between males and females, especially in relation to that of their matched controls. It would appear that the study of renal stone patients without regard to their sex may conceal important differences in dietary intake between patients and the normal stone free population.

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