

**PREDICTORS OF OSTEODYSTROPHY IN SUBJECTS
WITH CHRONIC NON-ALCOHOLIC PANCREATITIS WITH OR
WITHOUT DIABETES**

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DOI:10.4158/EP10410.OR

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ABSTRACT

Objective: To study bone mineral content (BMC), bone mineral density (BMD), Vitamin D status and bone mineral parameters in subjects with chronic non-alcoholic pancreatitis and to determine the relationship between pancreatic dysfunction and these parameters.

Methods: Thirty-one eligible non-alcoholic males with proven chronic pancreatitis and 35 control males were studied. Biochemical parameters, parameters of malabsorption and BMD of the lumbar spine were evaluated.

Results: In subjects with chronic pancreatitis the mean body mass index (BMI) was 18.46 (\pm 2.86) kg/m² and the median 25(OH) Vitamin D was 19.6(5.0 – 52.0) ng/ml. A higher proportion of patients had a T score of $< - 2.5$ (9/31, 29%) than controls (3/35, 9%). BMI correlated significantly with BMD ($r=0.426$; $P= 0.017$). There was an inverse correlation between stool fat and BMC ($r = \text{minus } 0.47$; $P=0.03$) in patients with chronic pancreatitis. There was no significant correlation between serum Vitamin D or biochemical parameters and BMD. Patients with steatorrhea had a significantly lowered BMC than subjects without steatorrhea and this difference could not be accounted for by differences in BMI, presence of diabetes or hypovitaminosis D.

Conclusions: Pancreatic osteodystrophy is a novel entity comprising osteopenia, osteoporosis and osteomalacia in patients with chronic pancreatitis. The inverse correlation between stool fat and BMC in subjects with chronic pancreatitis, the strong positive correlation between BMI and BMC and the lack of difference in BMC between vitamin D sufficient and deficient subjects, suggests that long-standing malabsorption with attendant chronic undernutrition is the major factor contributing to the changes in BMC.

Keywords: *Chronic Pancreatitis, Pancreatic Osteodystrophy, Bone Mineral Density*

INTRODUCTION:

Chronic Pancreatitis is a progressive condition in which permanent changes occur in the pancreas secondary to inflammation, leading to deficiency of pancreatic exocrine and endocrine functions (1). Tropical pancreatitis, prevalent in developing countries, is a form of chronic calcific non-alcoholic pancreatitis in younger patients who present with steatorrhea and/or diabetes mellitus (2,3). Many patients have abdominal pain, weight loss, symptoms of maldigestion and diabetes but some have a paucity of symptoms. Functional tests for pancreatic insufficiency (4) in the early stages of pancreatitis are of limited utility and biopsy of the pancreas for the diagnosis of pancreatitis is impractical. Calcifications within the pancreatic ducts or parenchyma—and/or dilated pancreatic ducts—combined with pancreatic atrophy are virtually pathognomonic of chronic pancreatitis and occur in 90% of those with late stage disease (5,6).

In chronic pancreatitis, the chronic inflammation, low body mass index (BMI), undernutrition, co-existing diabetes, poor sunlight exposure and decreased physical activity due to chronic illness are factors that may increase the risk of bone loss. Deficiency of fat-soluble vitamins is to be expected in patients with pancreatic insufficiency and steatorrhoea (1). Vitamin D enhances calcium absorption, mineralization of osteoid and osteoblastic activity and vitamin D deficiency leads to

reduced bone mineral density to an extent seen in osteopenia and osteoporosis before overt osteomalacia sets in. Osteoporosis leads to increased bone fragility and increases fracture frequency (7,8). There is limited knowledge about bone mineral status in chronic pancreatitis. In recent years a few groups have studied bone mineral density in chronic pancreatitis (9-11). These studies with small numbers of patients show variable prevalence of metabolic bone disease and vitamin D deficiency. One of these studies (9) shows a significant positive correlation between 25(OH) vitamin D levels and BMD at lumbar spine and worsening BMD with increasing severity of chronic pancreatitis. No prospective study so far has addressed the relative contribution of overall under nutrition, vitamin D deficiency, associated diabetes mellitus and the effect of chronic illness per se on the pathogenesis of pancreatic osteodystrophy. Long term studies on the fracture prevalence in these patients and the potential impact of interventions to improve bone health are unknown. With current treatment modalities patients with chronic pancreatitis with or without diabetes survive longer and awareness and early recognition of these skeletal problems may pave the way for interventional studies to improve bone health. The present study was therefore undertaken to assess the prevalence of osteoporosis in male subjects with non-alcoholic chronic pancreatitis and to evaluate potential contributing factors.

RESEARCH DESIGN AND METHODOLOGY:

Consecutive male patients aged between 20 and 60 years with proven chronic non-alcoholic pancreatitis attending the Endocrinology or Gastroenterology out-patient department were recruited (Fig. 1). Women, men with history of alcohol dependence (12), immobilized subjects, those with lower limb amputation, cardiovascular disease,

liver disease, renal disease, hypogonadism and subjects on drugs affecting bone metabolism (hormones, anti-epileptics, anti-TB drugs, diuretics, glucocorticoids and anti-resorptive drugs) were excluded.

Clinical assessment included: (a) detailed history of abdominal pain, steatorrhea, weight loss, bone pain, fractures, complications of diabetes, drug history, concomitant illness, (b) assessment of dietary calcium intake using an oral semi-quantitative food frequency questionnaire (13,14), (c) examination to look for complications of diabetes, proximal myopathy, signs of malnutrition, hypocalcaemia and skeletal deformities.

Fasting serum calcium, phosphate, alkaline phosphatase, albumin, creatinine, plasma glucose, and 24 hour urinary calcium, phosphorous and creatinine were measured by a fully automated, micro analyzer (HITACHI 912). Serum 25 (OH) Vitamin D was measured by RIA (Dia Sorin, Stillwater Minnesota). Patients were maintained on a high-fat diet (50 g/day) for 5 days (starting 2 days before stool collection) and 72-hour stool fat was estimated. **Stool fat excretion of ≥ 18 gms/day was considered abnormal** (15).

BMD was assessed by Hologic Machine DXA scanner (QDR 4500; Hologic, Inc, Waltham, MA, USA) at lumbar spine. We did not measure BMD at hip or forearm because of resource constraints. Daily calibration graphs were maintained using phantoms and the precision of measurement was 2%. The reference population was normal Caucasians (manufacturer's database). The results obtained in study subjects were compared with 35 subjects who were age and socioeconomic status matched normal lean male subjects without chronic pancreatitis or diabetes mellitus.

STATISTICAL ANALYSIS

The SPSS 11 software package was used. Pearson's correlation was used to study the relationship between normally distributed continuous variables. An independent Student's two-tailed t-test was used to compare the means of two continuous variables if they were normally distributed and nonparametric tests were used if their distribution was not normal. 'P'-values ≤ 0.05 was considered statistically significant. Linear regression was used to analyze the relationship between a dependent variable and one or more independent variables.

ETHICS

The study protocol was approved by the institutional review board. It conforms to the ethical guidelines of the "World Medical Association declaration of Helsinki – ethical principles for medical research involving human subjects" adopted by the 18th WMA general assembly, Helsinki, Finland, June 1964 as revised in Tokyo 2004 as reflected in a priori approval by the institutional review board. The study was approved and funded by the Institutional Research Committee (RC Minute No.5693).

RESULTS:

A total of 31 males were studied (Fig 1). The majority (91%) hailed from a middle class background, were gainfully employed and had unrestricted outdoor physical activity but sunlight exposure was not quantified in these subjects. All the patients had features of chronic pancreatitis documented either by ultrasonography, computed tomography or endoscopic retrograde cholangiopancreatography (ERCP). Eleven (35%) subjects had chronic pancreatitis of unknown etiology. Twenty subjects (65%) had pancreatic duct dilatation with ductal calculi and parenchymal atrophy suggesting tropical fibrocalculous pancreatitis. Of these twenty subjects, eleven had diabetes

(Fibrocalculous pancreatic diabetes). Some patients had irregular treatment with pancreatic enzymes in the past from other hospitals, but none of them had taken calcium and vitamin D supplements. The study subjects had not taken pancreatic enzymes for at least 3 months before presentation at our centre.

Abdominal pain and weight loss (50% of patients) were the most common symptoms. The median duration of symptoms of abdominal pain and/or steatorrhea was 72 months (range 3-300 months). BMD was found to have a significant correlation with the duration of symptoms [(r = 0.431; p = 0.016)]. A typical clinical history of steatorrhea was elicited in only 31% of the patients but 69% had steatorrhea (stool fat >18 gms in 72 hours). The mean Body Mass Index (BMI) was 18.46 kg / m² (Table 1) and 45 % of patients had a BMI <18 kg / m². All subjects had normal corrected serum calcium and phosphate values (Table 1). The mean renal threshold for phosphate (TMP/GFR) was (3.73 ± 0.68 mg/dl). The mean dietary calcium intake was lower [749 ± 170.15 mgs/day] than that recommended for normal healthy adults and 6.4 % of subjects had a dietary calcium intake <500 mgs. None of the patients had clinical features of overt osteomalacia such as bone pain or skeletal deformities. Furthermore, none of the subjects had clinical features of Vitamin A deficiency. The total 24 hour urine calcium value in most of our patients was either normal or low (Table 1).

Compared to normal healthy age and socio economic status matched adult males, our study subjects had significantly lower BMI and lower 25 (OH) vitamin D levels (p=0.020) and 24% of them had vitamin D deficiency (p= 0.04). Based on the current criteria (16), 16 (64%) of our subjects had 25(OH) vitamin D insufficiency or deficiency (< 20 ng/ml) and 6 (24%) had vitamin D levels < 10 ng/ml. Neither BMD (r

= 0.3; $p = 0.093$) nor BMC ($r = 0.298$; $p = 0.147$) was found to correlate significantly with 25(OH) vitamin D levels in the study subjects.

Nine (29%) patients with chronic pancreatitis had a T score < -2.5 as compared to 3(9%) age matched normal subjects ($p < 0.02$). The mean Bone Mineral Density (BMD) was $0.891(\pm 0.135)$ gm/cm² and the mean Bone mineral content (BMC) was $51.9(\pm 10.3)$ gms in subjects with chronic pancreatitis as compared to the values [(BMD = 0.946 ± 0.098 gm / cm² ($p = 0.69$); BMC = 50.51 ± 7.62 gms ($p = 0.54$)] in healthy controls. BMI correlated significantly (Fig. 2) with both BMD ($r = 0.523$; $P = 0.003$) and BMC ($r = 0.47$; $p = 0.017$) as has been described for normal subjects (17).

When compared with the subjects having a normal T-score (Table 2), those with T score < -2.5 were found to have a lower BMI ($p = 0.021$) and a trend towards higher stool fat excretion, but the 25(OH) Vitamin D levels were similar in the two groups.

Twenty one (68%) subjects had diabetes mellitus; of these 4 were on a diabetic diet, 4 were on oral diabetic agents and 13 subjects were on insulin. Four subjects had a family history of diabetes. The median duration of diabetes was 36 months (range 3 – 204). Subjects with diabetes had a lower mean BMI (17.7 ± 2.4 vs 20.0 ± 3.31 kg / m²; $p = 0.087$) (Table 3) than those without diabetes. Compared to nondiabetics, significant positive linear correlations were found between BMI and BMD ($r = 0.578$; $p = 0.006$; Fig 3) and BMI and BMC ($r = 0.448$; $p = 0.041$) only in subjects with diabetes mellitus. In subjects with diabetes, the median 25(OH) Vitamin D value (12.6 ng/ml; range 5 – 35) showed a non-significant trend to be lower than those without diabetes (20.15 ng/ml, range 15.5 – 52.1) ($p = 0.056$). The median 72 hour stool fat (25.2 gms; range 9.7 – 93.7) among subjects with pancreatic diabetes was higher than the median

value (12.55 gms, range 12.30 – 28.60) among those without diabetes but this difference was not ($p = 0.417$) statistically significant.

In those with steatorrhea, the 25 (OH) vitamin D levels, BMI and BMD had a non-significant trend to be lower while BMC was significantly lower (Table 4) than those without steatorrhea ($p = 0.010$). There was a significant negative correlation ($r = \text{minus } 0.468$; $p = 0.028$; Fig 4) between stool fat and BMC but the correlation between stool fat and BMD did not achieve statistical significance ($r = \text{minus } 0.386$; $p = 0.076$). Patients with steatorrhoea had a significantly lower BMC (45.6 ± 5.47) than age matched controls (56.3 ± 12.5 ; $p = 0.010$).

When a linear regression analysis pooling both the cases and controls was done to see if other factors contributed to the low BMD, BMI alone was found to have a significant correlation [$r = 0.361$; $p = 0.003$] but 25(OH)Vitamin D levels [$r = 0.220$; $p = 0.092$], dietary calcium [$r = 0.233$; $p = 0.06$] and urinary calcium levels [$r = \text{minus } 0.029$; $p = 0.819$] did not show any correlation.

DISCUSSION:

Chronic pancreatitis with or without diabetes is a relatively common problem in India and other tropical countries (18,19). While it is well known that patients with Type 1 diabetes have a low bone mineral density (20), BMD has not been extensively studied in chronic pancreatitis and associated diabetes mellitus. However there are a few reports which indicate that skeletal problems do occur in these patients.

The reported prevalence of low BMD (29%) in our subjects with chronic pancreatitis is nearly 1.5-2 times the prevalence of osteoporosis (14-19%) reported in Type 1 Diabetes mellitus (21,22). Unlike the situation in Type 1 diabetes mellitus

where BMD has been shown to correlate with duration and the severity of diabetes mellitus (23) we did not find such a correlation in our subjects with chronic pancreatitis and secondary diabetes mellitus. Patients with FCPD are not entirely insulin deficient and this may be one reason why they differ from Type 1 diabetics with regards to their skeletal problem. The combination of steatorrhoea, associated weight loss and related vitamin D deficiency may predispose these patients to an even greater skeletal problem than just Type 1 diabetes mellitus.

In the present prospective study, we find that patients with chronic pancreatitis with or without associated diabetes mellitus have a state of chronic undernutrition with very low BMI compared with age and socioeconomic status matched controls (18.46 kg/m² Vs 22.6 kg/m²) and nearly half the number of our study subjects (14/31,45%) have a BMI <18 kg/m². Our subjects with chronic pancreatitis and T score < minus 2.5 had a significantly lower BMI ($P=0.029$) than those with T score > minus 2.5. This observation along with the strong positive correlation seen between BMI and BMD ($P=0.003$) implies that the chronic undernutrition in these subjects is an important contributor to the skeletal problem. The mean BMD ($p = 0.597$) and BMC ($p = 0.526$) of subjects with chronic pancreatitis and diabetes were not significantly lower than in their non-diabetic counterparts suggesting that the presence or absence of diabetes mellitus may not be an important determinant of BMD in this disorder. However even amongst patients with chronic pancreatitis and diabetes mellitus we find significant positive linear correlations between BMI and BMD ($r=0.578$; $p =0.006$) and BMI and BMC($r=0.448$; $p=0.041$) indicating the importance of overall undernutrition as reflected by low BMI as a determinant of bone mineral density.

In our subjects, both BMD and BMC correlated significantly with BMI. Only BMC correlated negatively with the 72 hour stool fat in our study subjects [BMC ($r = \text{minus } 0.468$; $p = 0.028$). BMD did not show such a correlation ($r = \text{minus } 0.386$; $p = 0.076$)]. This lack of correlation between BMD and 72 hour stool fat could be due to the inherent differences between these two parameters representing bone strength.

Even though the majority of studies have used Bone mineral density (BMD) for defining osteoporosis, areal bone mineral density does not take the volume of bone into consideration when assessing the bone strength. This would be a paradox as bone strength is related to bone volume also. Therefore Heaney (24) argues that studies assessing bone strength should present Bone mineral content (BMC).

Our study confirms that among patients with chronic pancreatitis, those with exocrine pancreatic deficiency and steatorrhea are a subgroup with the most severe reduction in BMC while those without steatorrhoea seem to be relatively protected. The significant inverse correlation between stool fat content and lumbar spine BMC in the entire group further strengthens our argument that chronic undernutrition is a major determinant of BMD and BMC in chronic pancreatitis. It is known that adipose tissue is an important source of estrogen in both sexes and it is possible that the lack of adipose tissue is partly responsible for the skeletal problem. These undernourished subjects have poor muscle mass as well and this could be an additional important contributing factor (25,26).

Depending on the criteria used to define Vitamin D deficiency, 64 % of our subjects with chronic pancreatitis had biochemical evidence of vitamin D insufficiency or deficiency. Our observation that patients with chronic pancreatitis and steatorrhoea

have a lower mean 25(OH) vitamin D level is in agreement with the observations of Mann et al (9). In our study nearly one fourth of subjects with chronic pancreatitis had severe vitamin D deficiency and overall the mean 25(OH) vitamin D level was significantly lower in the study subjects. However we were unable to find a significant correlation between 25(OH) vitamin D levels and BMD or BMC at the lumbar spine. We did not measure BMD at femoral neck or distal radius. It is possible that low 25(OH) Vitamin D levels may be selectively related to BMD at these sites. Overall our findings imply that chronic overall malnutrition rather than selective vitamin D deficiency may be more important in the pathogenesis of pancreatic osteodystrophy.

Metabolic bone diseases are potentially treatable co-morbidities in chronic pancreatitis. With appropriate treatment for their diabetes and pancreatic malabsorption these patients live longer and are at risk for skeletal problems during their extended life-span. Paying critical attention to their nutrition and restoration of ideal body weight while maintaining optimal glycemic control may be of crucial importance in optimizing bone health in these subjects. Awareness of the magnitude of the skeletal problem in chronic pancreatitis and appropriate evaluation are important steps in the identification and management of patients at risk for pathological fractures.

We have studied only a small number of these subjects and prospective long-term studies in larger numbers of these patients with built in interventional strategies are warranted.

CONCLUSIONS:

- 1.** Among male subjects with chronic non-alcoholic pancreatitis, at a mean age of 36 years, 29% had a T-score of < minus 2.5 and 32% had a T-score between minus 1 and minus 2.5.
- 2.** Compared to controls they have a significantly lower BMI and 25(OH) vitamin D levels.
- 3.** Subjects with chronic pancreatitis and steatorrhoea had a significantly reduced BMC compared to similar subjects without steatorrhoea. This difference could not be accounted for by presence or absence of either diabetes mellitus or vitamin D deficiency. Subjects with chronic pancreatitis and a T score less than minus 2.5, had a significantly lower BMI, showed a trend towards higher stool fat excretion, but did not have lower mean 25 (OH) Vitamin D levels.
- 4.** In subjects with diabetes with chronic pancreatitis, there was a linear correlation between BMI and BMD but no correlation between 25 (OH) Vitamin D levels and BMD or BMC.
- 5.** Overall undernutrition in chronic pancreatitis rather than vitamin D deficiency may be an important determinant of BMD and BMC in these subjects.
- 6.** Pancreatic osteodystrophy in chronic pancreatitis is an under recognized co-morbidity requiring further study.

Acknowledgements

Dr. Mathew John & Dr. Asha, Department of Endocrinology

Kavitha, Department of Biostatistics,

Sarah Jacob, Department of Nutrition & Dietetics

Ms Bhanu for all the secretarial assistance and all the study participants.

This study was funded by a Research Grant from the Christian Medical College, Vellore.

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Table 1 - Demographic characteristics & Biochemical parameters

Characteristic *	Cases (n = 31) Mean (SD)	Controls (n = 35) Mean (SD)	P
Age (years)	35.8 (9.0)	38.6 (5.2)	0.128
Weight (kg)	51.2 (9.3)	64.3 (9.3)	0.001
BMI (kg/meter ²)	18.46 (2.86)	22.6 (3.1)	0.001
Sr. Calcium § (corrected) (8.3 – 10.5 mg %)	9.02 (0.37)	8.61 (0.29)	0.001
Sr. Phosphate § (2.5 – 4.6 mg %)	3.93 (0.58)	3.64 (0.54)	0.001
Creatinine (0.5 – 1.4 mg %)	0.94 (0.15)	0.99 (0.11)	NS
Alk. Phosphatase (40 – 125 U/L)	114.4 (52.7)	77.3 (17.8)	0.001
Urine calcium # (50 – 300 mg/24 hrs)	157 (15 – 492) †	67 (4 -235) †	0.001
TMP / GFR (2.5 – 5.0 mg / dl)	3.73 (0.68)	3.4 (0.85)	NS
Stool fat (< 18 gms /72 hrs)	22.8 (9.70 – 93.70) †	Not done	
72 hrs stool volume (< 600 gms)	1320.9 (598.52)	Not done	
Vitamin D (>20 ng/ml)	15.5 (5.0 – 52.0) †	22.2 (5.6)	0.020
BMD gm/cm ²	0.891(0.135)	0.946 (0.098)	0.052
BMC gm/cm	51.9 (10.3)	50.51(7.62)	0.540

Note : † Median and range * Numbers represent normal laboratory ranges

Three cases had a urinary calcium values of 375,397 & 492 mg/24 hour urine respectively, resulting in a median of 157mg/24 hour urine. If these values are excluded, the median value is 134mg and this is still significantly higher than the controls (p=0.003). These three patients did not have significant bone disease or renal calculi.

§ Even though the cases had a higher serum corrected calcium and phosphate levels, the values were within the normal range and none had hypercalcemia.
The reason for these differences in the urinary calcium and serum calcium, phosphate values between the cases and controls is not clear.

Table 2: Comparison of subjects with and without abnormal BMD

	Subjects with T-score between minus 1 and minus 2.5		Subjects with T-score of < minus 2.5		P-value
	Mean	SD	Mean	SD	
BMI (kg/m²)	19.40	2.48	16.17	2.51	0.029
BMC (gm)	56.04	9.07	41.77	4.46	0.001
BMD (gm/cm²)	0.952	0.103	0.742	0.06	0.001
Vit.D (ng/ml)	21.5 †	5-52	16.97	8.80 – 29.1	0.77
72 hour stool fat	19.15 †	10.50 – 29.20	36.06	9.70 – 93.66	0.059

† Median and range

Table 3: Comparison of subjects with and without diabetes mellitus

	Subjects with diabetes		Subjects without diabetes		P
	Mean	SD	Mean	SD	
Age (years)	37.3	9.4	32.6	7.7	0.228
Wt (Kg)	48.7	7.9	56.5	10.3	0.036
BMI (kg/m ²)	17.7	2.4	20.0	3.31	0.087
Corrected Calcium (mg %)	8.98	0.36	9.1	0.41	0.230
25(OH)Vit.D (ng/ml)	12.60	(5.0 - 35.8)	20.15	(15.5 - 52.1)	0.056
72 hour Stool Vol (gms) †	1360	686.5	1216.6	269.6	0.941
72 hour Stool fat (gms) †	25.2	(9.7 – 93.7)	12.55	(12.3 – 28.6)	0.417
Alkaline Phosphatase (U/L)	121	60.1	99.5	30.9	0.235
BMD (gm/cm ²)	0.873	0.147	0.902	0.110	0.597
BMC (gm/cm)	51.88	11.56	51.9	7.52	0.526

† Median and range

Table 4: Comparison of subjects with and without Steatorrhea

	Subjects with steatorrhea		Subjects without steatorrhea		
	Mean	SD	Mean	SD	P-value
BMI (kg/m²)	17.7	2.24	19.34	3.22	0.230
25(OH)Vit.D (ng/ml)	13.35	(6.9- 31.0)	17.85	(7.5- 52.1)	0.487
BMD (gm/cm²)	0.822	0.09	0.93	0.16	0.095
BMC (gm)	45.6	5.47	56.3	12.5	0.010
72 hour Stool fat (Gms)	28.4	(21.4- 93.7)	12.4	(9.7- 17.4)	0.004

Figure 1: Flow chart showing study patient characteristics

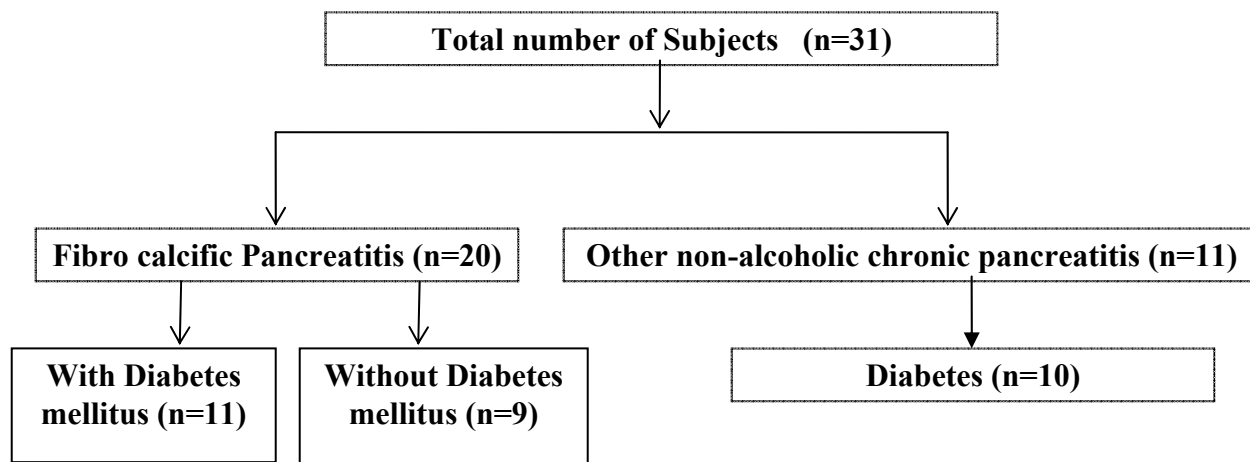


Figure 2: Correlations of Body mass index with BMD and BMC by linear regression

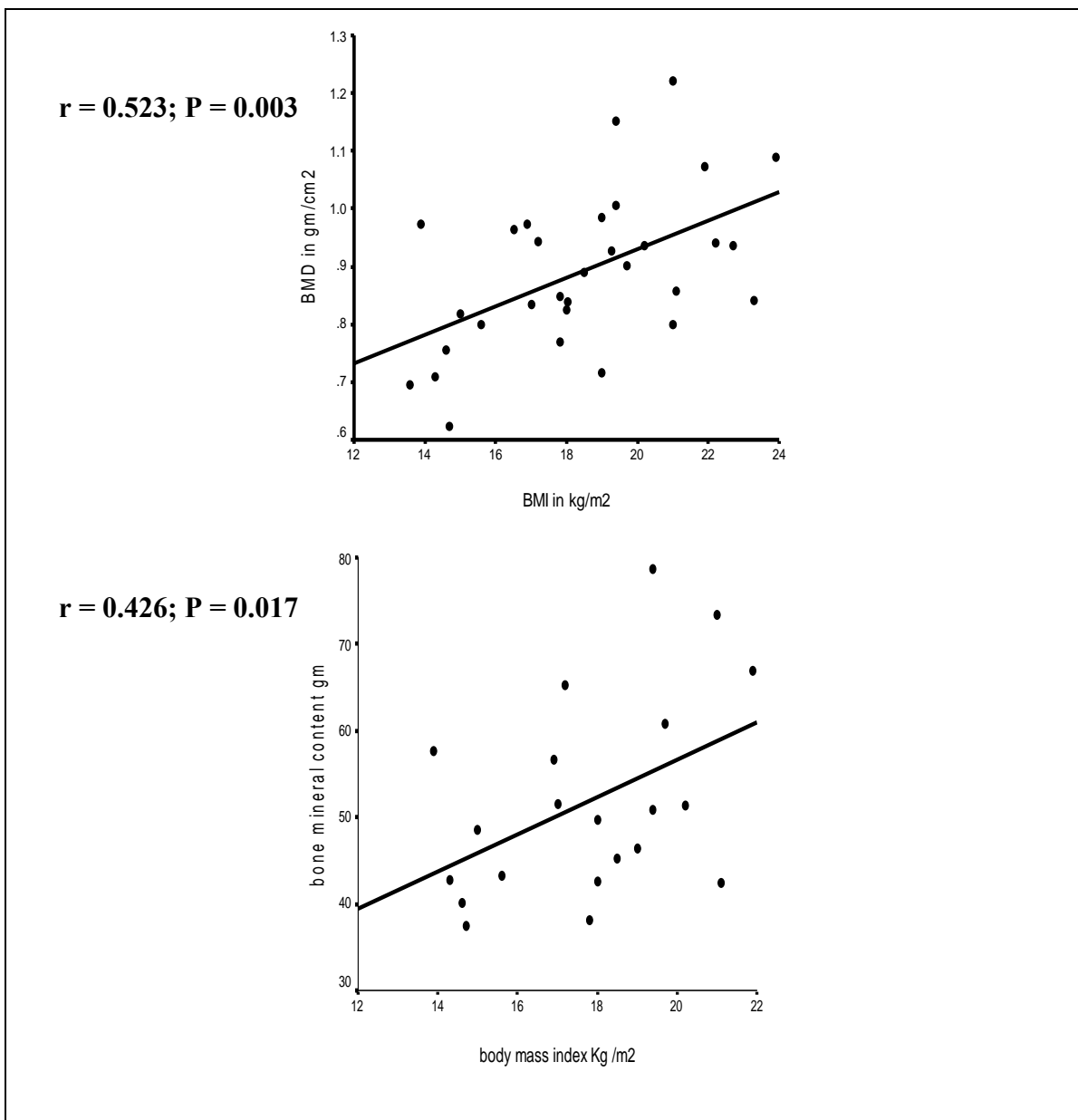


Figure 3: Correlations - BMD and BMI (diabetic subjects)

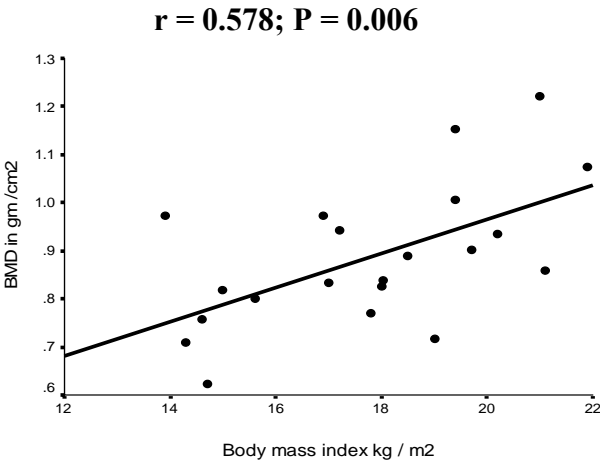


Figure 4: Correlation between stool fat and BMC in subjects with steatorrhea

