abortions. And if this were true then women with high hormone concentrations would have a lower fecundity than other women (taking more time to become recognisably pregnant because of unrecognised spontaneous abortions). This thesis seems to be false, however, because DZ twins (who themselves tend to be conceived when gonadotrophin concentrations are high) take less, not more, time to conceive than singletons.[17 18]

This work was supported by the National Fund for Research into Crippling Diseases. I thank Miss Talat Jamil and Dr Anne McLaren for help and encouragement.

References

[1] James WH. Time of fertilisation and sex of infants. *Lancet* 1980;i:1124-6.
[2] Guerrero R. Association of the type and time of insemination within the menstrual cycle with the human sex ratio at birth. *N Engl J Med* 1974;**291**:1056-9.
[3] Harlap S. Gender of infants conceived on different days of the menstrual cycle. *N Engl J Med* 1979;**300**:1445-8.
[4] Wyshak G. Statistical findings on the effects of fertility drugs on plural births. *Prog Clin Biol Res* 1978;**24B**:17-33.
[5] Hack M, Brish M, Serr DM, Insler V, Lunenfeld B. Outcome of pregnancy after induced ovulation. *JAMA* 1970;**211**:791-7.
[6] Adashi EY, Rock JA, Sapp KC, Martin EJ, Wentz AC, Jones GS. Gestational outcome of clomiphene-related conceptions. *Fertil Steril* 1979;**31**:620-6.
[7] Healy DL, Burger HG. An hypothesis for high multiple pregnancies after clomiphene. *Aust NZ J Obstet Gynaecol* 1978;**18**:242-6.
[8] Karow WG, Payne SA. Pregnancy after clomiphene citrate treatment. *Fertil Steril* 1968;**19**:351-62.
[9] Caspi E, Ronen J, Schreyer P, Goldberg MD. The outcome of pregnancy after gonadotrophin therapy. *Br J Obstet Gynaecol* 1976;**83**:967-73.
[10] Lachelin GCL, Brant HA, Swyer GIM, Little V, Reynolds EOR. Sextuplet pregnancy. *Br Med J* 1972;i:787.
[11] Lauersen NH, Buchman M, Beling CG. Successful quadruplet pregnancy following ovulation induced with human menopausal gonadotrophin and human chorionic gonadotrophin. *Acta Obstet Gynecol Scand* 1974;**53**:387-91.
[12] Ansbacher R. The induction of ovulation with FSH and HCG. *Milit Med* 1973;**138**:149-51.
[13] Monnier JC, Lanciaux B, Boulogne M, *et al.* Problèmes posés par la surveillance d'une grossesse quintuple. *Revue Française de Gynécologie et d'Obstétrique* 1980;**75**:219-25.
[14] Schenker JG, Laufer N, Weinsten D, Yarkoni S. Quintuplet pregnancies. *European Journal of Obstetrics, Gynaecology and Reproductive Biology* 1980;**10**:257-68.
[15] Schenker JG, Simha A. Quintuplet pregnancy. *Obstet Gynecol* 1975;**45**:590-3.
[16] Senez P, Gillet JY. Avenir et qualité des grossesses obtenues par l'association citrate de clomifène et gonadotrophine chorionique. A propos de 53 cas en série continue. *J Gynecol Obstet Biol Reprod (Paris)* 1978;**7**:987-90.
[17] Bulmer MG. The effect of parental age, parity and duration of marriage on the twinning rate. *Ann Hum Genet* 1959;**23**:454-8.
[18] Pollard GN. Multiple births in Australia 1944-63. *J Biosoc Sci* 1969;**1**:389-404.

(*Accepted 31 July 1980*)

SHORT REPORTS

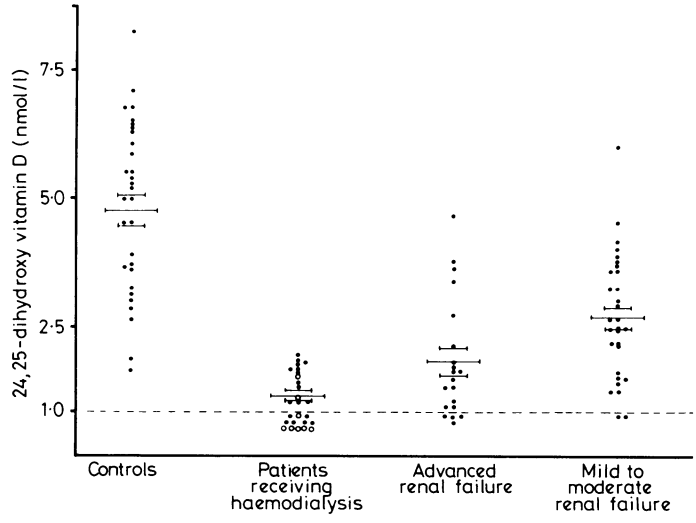
Serum concentrations of 24,25-dihydroxy vitamin D in different degrees of chronic renal failure

Decreased production of 1,25-dihydroxy vitamin D in advanced renal failure may be a major factor in the pathogenesis of renal osteodystrophy.[1] Recent studies have shown that another renal metabolite, 24,25-dihydroxy vitamin D, is important in normal bone formation.[2] We have measured the serum concentrations of 25-hydroxy and 24,25-dihydroxy vitamin D in patients with different degrees of renal failure to provide further data concerning vitamin D metabolism in chronic renal failure.

Patients, methods, and results

Serum concentrations of 25-hydroxy and 24,25-dihydroxy vitamin D were measured in 76 patients with chronic renal failure and 30 controls. The patients comprised 26 undergoing chronic haemodialysis three times a week (including eight anephric patients), 20 with advanced renal failure not requiring haemodialysis (creatinine clearances 10-35 ml/min/1·73 m^2), and 30 with early to moderate renal failure (creatinine clearances 40-80 ml/min/1·73 m^2). Serum samples from the patients receiving haemodialysis were obtained immediately before dialysis. The patients had not received transfusions within six weeks before the specimens were collected. No patient was receiving vitamin D supplements or drugs known to alter vitamin D metabolism. Concentrations of 25-hydroxy and 24,25-dihydroxy vitamin D were measured by competitive protein-binding radioassays[3] after preparative Sephadex LH-20 column and high-pressure liquid chromatography.

The mean (± SEM) serum concentration of 25-hydroxy vitamin D was significantly ($p<0·01$) lower in patients receiving haemodialysis (36·0±3·8 nmol/l (14·4±1·5 ng/ml)) than controls (53·8±3·6 nmol/l (21·5±1·4 ng/ml)). The mean concentrations in patients with advanced renal failure not requiring haemodialysis (43·5±5·3 nmol/l (17·4±2·1 ng/ml)) and in patients with mild to moderate renal failure (47·6±3·6 nmol/l (19·0±1·4 ng/ml)) did not differ from that in controls. The mean serum concentration of 24,25-dihydroxy vitamin D (figure) and the mean ratio of serum concentrations of 24,25-dihydroxy vitamin D to those of 25-hydroxy vitamin D were significantly lower ($p<0·01$) in the patients receiving haemodialysis (1·18±0·40 nmol/l (0·5±0·16 ng/ml) and 0·030±0·003 respectively), the patients with advanced renal failure not requiring haemodialysis (1·88±0·25 nmol/l (0·75±0·1 ng/ml) and 0·042±0·004 respectively), and the patients with mild to moderate renal failure (2·70±0·22 nmol/l (1·1±0·09 ng/ml) and 0·058±0·003) compared with the controls (4·78±0·30 nmol/l (1·9±0·12 ng/ml) and 0·092±0·004). The ratios of the two metabolites were directly correlated ($r=0·72$, $p<0·05$) with the creatinine clearances when data from all patients were analysed.



Mean ± SEM serum concentrations of 24,25-dihydroxy vitamin D in patients with different degrees of chronic renal failure and controls. ○ = Anephric patients.
Conversion: SI to traditional units—24,25-Dihydroxy vitamin D: 1 nmol/l ≈ 0·4 ng/ml.

Comment

Our results show that serum concentrations of 24,25-dihydroxy vitamin D are depressed in mild to moderate chronic renal failure and are low or undetectable in patients receiving dialysis. Reduced production of 1α, 25-dihydroxy vitamin D by the diseased kidney is generally believed to be important in the pathogenesis of renal osteodystrophy, and the serum concentration of this metabolite is

extremely low in advanced renal failure; the concentration is normal or increased, however, in patients with early to moderate renal failure, in whom hypocalcaemia, secondary hyperparathyroidism, and defective bone mineralisation are often present.[4] Furthermore, treatment with 1α,25-dihydroxy or 1α-hydroxy vitamin D_3 might alleviate skeletal pain, increase serum calcium concentration, suppress secondary hyperparathyroidism, and improve the skeletal lesions of osteitis fibrosa; results in patients with osteomalacia, however, were disappointing.[5] The question remains, therefore, whether another metabolite of vitamin D, important for normal bone structure, is affected in renal failure. 24,25-Dihydroxy vitamin D may possibly play a part in normal bone formation.[2] Our findings show that production of this metabolite is already impaired in early stages of renal failure. If low serum concentrations of 24,25-dihydroxy vitamin D are causally related to the osteomalacia of chronic renal failure, treatment with both 1,25-dihydroxy and 24,25-dihydroxy vitamin D may be needed to prevent and heal renal osteodystrophy.

We thank Reuven Terdiman for his help in the statistical analysis. This study serves as part of the requirements for the MD degree for L Leib at the Technion, Israel Institute of Technology, Faculty of Medicine.

[1] Mawer EB, Backhouse J, Taylor CM, Lumb GA, Stanbury SW. Failure of formation of 1,25-dihydroxycholecalciferol in chronic renal insufficiency. *Lancet* 1973;i:626-8.
[2] Ornoy A, Goodwin D, Noff D, Edelstein S. 24,25-dihydroxyvitamin D is a metabolite of vitamin D essential for bone formation. *Nature* 1978;**276**:517-9.
[3] Weisman Y, Reiter E, Root A. Measurement of 24,25-dihydroxyvitamin D in sera of neonates and children. *J Pediatr* 1977;**91**:904-7.
[4] Slatopolsky E, Gray R, Adams ND, *et al*. The pathogenesis of secondary hyperthyroidism in early renal failure. In: Norman AW, Schaefer K, Herrath DV, *et al*, eds. *Vitamin D basic research and its clinical application*. Berlin and New York: W de Gruyter, 1979:1209-15.
[5] Pierides AM, Ellis HA, Simpson W, Dewar JH, Ward MK, Kerr DNS. Variable response to long-term 1α-hydroxycholecalciferol in haemodialysis osteodystrophy. *Lancet* 1976;i:1092-5.

(*Accepted 19 May 1980*)

Vitamins Research Laboratory, Municipal Government Medical Centre, Tel-Aviv, Israel
Y WEISMAN, MD, lecturer
Z EISENBERG, MSC, technician
L LEIB, MD, physician
A HARELL, MD, professor

Nahariya Government Hospital, Nahariya, Israel
S M SHASHA, MD, physician

Biochemistry Department, Weizmann Institute of Science, Rehovot, Israel
S EDELSTEIN, PHD, senior scientist

Jet injection of insulin: comparison with conventional injection by syringe and needle

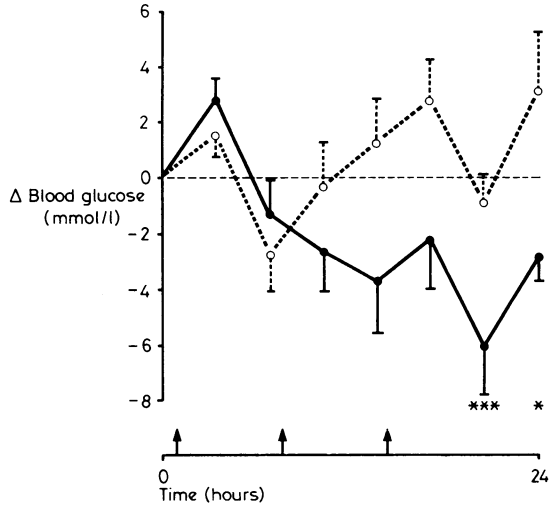
Achieving good control of blood glucose concentration in diabetes is important[1 2] but may be complicated by patients' reluctance to accept multiple injections of insulin and difficulty in synchronising carbohydrate and insulin absorption. Jet injection is reportedly less painful[3] and may provide faster absorption of insulin than standard syringe and needle.[3 4]

Patients, methods, and results

Thirteen insulin-dependent inpatient diabetics aged 17-18 were studied. Ten were receiving short-acting and intermediate-acting insulins twice daily and three once daily. All patients were stable for 48 hours before the study and were allocated alternately to group 1 (insulin injected by syringe and needle on day 1 and by injector gun on day 2) or group 2 (injector gun on day 1 and syringe and needle on day 2). Jet injections were given using the Med-E-Jet device (Med-E-Jet Limited, Wrexham, Clwyd). Identical insulin doses were administered on both days by the same doctor 15 to 30 minutes before breakfast or evening meal. Short-acting and intermediate-acting insulins were injected separately.

On each day blood glucose was measured before meals, one hour after meals, and before retiring. Medical staff scored bleeding and insulin leakage from each injection site as none (0), drop (1), and trickle (2). Patients scored pain at the time of injection and pain over the hours after injection as none (0), slight (1), moderate (2), severe (3). Student's *t* test (paired or unpaired) and Wilcoxon's matched pairs signed ranks test were used as appropriate for statistical analysis.

Complete blood glucose profiles were obtained on nine patients, five in group 1 and four in group 2. Mean blood glucose values (±SEM) were initially similar in the two groups (8·4±1·1 mmol/l and 9·6±1·4 mmol/l (151±20 mg/100 ml and 173±25 mg/100 ml) respectively) (NS). By 24 hours the mean blood glucose concentration had fallen in the group treated initially with the syringe but had risen in the group treated with the injector gun (6·0±0·8 mmol/l versus 13·3±2·1 mmol/l (108±14 mg/100 ml versus 239±38 mg/100 ml)) ($p<0·01$). After a further 24 hours, following the change in injection technique, mean blood glucose values had again risen with jet injection but fallen with syringe injection (8·7±3·2 mmol/l versus 9·8±2·0 mmol/l) (157±58 mg/100 ml versus 176±36 mg/100 ml)) (NS). On paired testing the change in blood glucose from the fasting value on each of the study days was significantly different between the two techniques before bedtime ($n=9$; $p<0·01$) and fasting the next day ($n=9$; $p<0·05$) (figure).



Change in blood glucose (±SEM) from fasting value at beginning of day after injection by syringe (●) and gun(o). Main meals indicated by arrows. Significance of differences: *$p<0·05$; ***$p<0·01$. (Blood glucose: 1 mmol/l≈18 mg/100 ml.).

Total scores after injection by syringe and gun respectively were 21 versus 9 for immediate pain, but 5 versus 13 for delayed pain. Bleeding was scored 19 versus 31 ($p<0·05$) and insulin leakage 17 versus 14. Overall six patients preferred the syringe and needle, four preferred the jet injector gun, and three were ambivalent.

Comment

The results clearly showed a rise in blood glucose values at 24 and 48 hours when using the injector gun but a corresponding fall when using the conventional syringe. Thus the effect of insulin given by jet injection was shorter lasting than an equivalent dose given by syringe. Absorption may be faster after jet injection owing to dispersion of the insulin, which may be a useful advantage of the technique. In this small study, however, the differences in blood glucose values between the two methods over the hours immediately after injection were not significantly different. The results emphasise that adjustment of insulin dosage will probably be necessary when altering the method of insulin administration. The advantage of less immediate pain with the injector gun was offset by more delayed pain and also more bleeding. From the relatively few injections received the patients expressed no clear preference for this expensive new technique.

This study provided no definite evidence to favour use of this particular injector gun over conventional syringe and needle. This conclusion may need to be revised when the results of studies of insulin absorption are available.

We are grateful to the British Diabetic Association for financial aid. RW