Papers

Systematic review of role of polymerase chain reaction in defining infectiousness among people infected with hepatitis C virus

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Abstract

Objective: To assess the role of polymerase chain reaction in defining infectiousness among people infected with hepatitis C virus.
Design: Published studies of hepatitis C transmission were examined. Twenty nine studies with identified sources of hepatitis C infection who were tested for presence of hepatitis C RNA by polymerase chain reaction were reviewed, including studies of vertical transmission (n = 21), transmission after transplantation (n = 3), transfusion of blood components (n = 3), and needlestick exposure (n = 2).
Subjects: All patients identified in studies.
Results: A total of 2022 people who had been exposed to sources positive for antibody to hepatitis C were identified. Among 1148 people exposed to sources positive by polymerase chain reaction 148 cases of transmission occurred compared with no definite case among 874 people exposed to negative sources. Rates of transmission from positive sources were 6.2% for perinatal exposure, 6.1% after needlestick exposure, 78% after solid organ or bone marrow transplantation, and 83% after transfusion of blood components. Other factors influencing risk of vertical transmission were coinfection with HIV and level of hepatitis C viraemia.
Conclusions: Negative results by polymerase chain reaction indicate an extremely low probability of transmission of hepatitis C from a person with antibody to hepatitis C.

Introduction

Since the discovery of hepatitis C virus[1] and development of a diagnostic assay to detect antibodies against it[2] the major pathways of transmission have been reasonably well defined.[3] [4] Needle sharing among injecting drug users and transfusion of blood products before the introduction of screening for hepatitis C have accounted for most such infections in developed countries. Other modes of parenteral transmission (non-sterile medical and dental equipment, needlestick exposure in the healthcare setting, and tattooing) and mother to child transmission occur, but their population impact has not been reliably estimated.[3] Sexual and household contact have been the subject of conflicting reports as to their likelihood of transmission of the virus.[5-8]

A key issue that arises in the management of people positive for antibody to hepatitis C is their risk of transmitting the virus by one or more of the above routes. For example, counselling of a pregnant woman positive for hepatitis C antibody would be aided by a clearer understanding of risk factors for vertical transmission. Advice to healthcare workers on their level of risk after needlestick injuries from an infected patient and policy making with regard to healthcare workers positive for the virus would also be helped by an improved understanding of the risk of transmission in these settings.

The development of polymerase chain reaction methods for detecting hepatitis C RNA[9] [10] has provided a potential means of assessing infected people in terms of their infectiousness. Factors such as level of hepatitis C viraemia and HIV coinfection may also be predictive of risk of transmission. With the goal of estimating the role of such factors in various settings we undertook a review of published studies of hepatitis C transmission.

Methods

We sought all published studies which examined transmission of hepatitis C from patients positive for the virus who were tested for evidence of hepatitis C viraemia by polymerase chain reaction for hepatitis C RNA. Studies were identified through searches of Medline and Embase databases to January 1997 and from the bibliographies of published papers. Studies were included if results of polymerase chain reaction for sources of exposure to hepatitis C were recorded. Transmission rates were calculated separately for sources with positive and negative results. Pooled estimates of hepatitis C transmission rates were calculated for different modes of transmission, with transmission rates from individual studies weighted according to sample size. Additional information such as level of hepatitis C viraemia and coinfection with HIV was also sought and the effect of these factors on transmission efficiency examined.

Identification of hepatitis C antibody was generally with enzyme linked immunosorbent assay (ELISA), often with confirmatory recombinant immunoblot

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assay (RIBA), although first, second, and third generation assays were used in various studies. Detection of hepatitis C RNA was by polymerase chain reaction with primers derived from the 5' non-coding region of the hepatitis C genome. Most studies used "in house" polymerase chain reaction technology with nested primers. Both in house non-nested primers or commercial polymerase chain reaction kits (Roche, Amplicor), or both, however, were used in a few studies. Quantitation of hepatitis C RNA, when performed, used either branched DNA or competitive polymerase chain reaction methods.

Results

A total of 29 articles published between 1992 and 1996 fulfilled the above criteria; 21 of these studies examined vertical hepatitis C transmission [11-31] with the remainder examining hepatitis C transmission after bone marrow or solid organ transplantation (n = 3),[32-34] transfusion of blood components (n = 3),[35-37] and needlestick exposure (n = 2).[38 39]

Vertical transmission studies
In vertical transmission studies, which included mothers who were positive for hepatitis C by polymerase chain reaction and mothers who were negative (n = 18), the percentage of mothers with positive results varied from 33% to 94%, with a pooled estimate of 54% (table 1). Three additional studies selected only those mothers with proved chronic hepatitis C infection.[12 17 20]

Among 903 children born to mothers positive for hepatitis C by polymerase chain reaction the rate of transmission of hepatitis C varied from 0% to 42%, with a combined rate of 6.2% (95% confidence interval 4.6% to 7.8%). In contrast, no case of transmission was reported among 735 children born to mothers negative by the reaction (0.0% to 0.4%) (table 1). Among positive mothers other factors which were reported to influence transmission were level of viraemia,[17 18 20 25 28] coinfection with HIV,[19 25 26] and method of delivery.[19] The pooled transmission rate for hepatitis C from mothers positive for HIV and hepatitis C antibody was 15.8% (11.8% to 19.8%). In contrast, a transmission rate of 1.9% (1.2% to 2.6%) for hepatitis C was seen among children born to mothers who were seronegative for HIV or of unknown status. In five of seven vertical transmission studies in which measurement of hepatitis C viraemia was performed, transmission was associated with higher level viraemia.[17 18 20 25 28] One study demonstrated a significantly higher transmission rate among vaginally delivered infants compared with infants delivered by caesarean section (32% v 6%)[19] but showed no association between risk of transmission and breast feeding. Hepatitis C genotype and maternal alanine transferase activity did not correlate with risk of transmission in those studies where these factors were assessed.

Other transmission studies
The three studies examining transmission of hepatitis C from transplant donors positive for hepatitis C anti-

Table 1 Studies on vertical transmission of hepatitis C with information on hepatitis status by polymerase chain reaction among mothers

Study	No of subjects (mother/infant)	Source positive by polymerase chain reaction (%)	Transmission of hepatitis C (proportion (%))		
			Positive by polymerase chain reaction	Negative by polymerase chain reaction	Positive for antibody to HIV and hepatitis C
Pipan 1996 (Italy)	25/25	72	0/18	0/7	No HIV
Sabatino 1996 (Italy)	30/30	33	3/10 (30)	0/20	No HIV
Fischler 1996 (Sweden)	55/58	75	0/40	0/18	0/2
Matsubara 1995 (Germany)	29/31	66	3/21 (14)	0/10	No HIV
Giacchino 1995 (Italy)	31/31	61	2/19 (11)	0/12	No HIV
Zuccotti 1995 (Italy)	37/37	57	6/21 (29)	0/16	4/20 (20)
Zanetti 1995 (Italy)	116/116	55	8/64 (13)	0/52	8/22 (36)
Resti 1995 (Italy)	22/22	55	5/12 (42)	0/10	No HIV
Power 1995 (Ireland)*	545/840	46	7/386† (2)	0/454†	NA
Meisel 1995 (Germany)*	55/55‡	57	1/23 (4)	0/32	No HIV
Manzini 1995 (Italy)	45/45	63	0/27	0/16	1/18 (6)§
Moriya 1995 (Japan)	84/87	100¶	2/87 (2)	—	No HIV
Paccagnini 1995 (Italy)	37/37[1]	62	9/23 (39)	0/14	12/53 (23)
Ohto 1994 (Japan)	53/54	58	3/32 (9)	0/22	NA
Lin 1994 (Taiwan)	15/15	100¶	1/15 (7)	—	No HIV
Roudot-Thoraval 1993 (France)	17/18	47	0/8	0/10	No HIV
Uehara 1993 (Japan)	12/12	58	1/7 (14)	0/5	NA
Kurauchi 1993 (Japan)	16/16	94	0/15	0/1	No HIV
Lam 1993 (Scotland)‡	56/66	59	4/38 (11)	0/28	3/58 (5)
Wejstal 1992 (Sweden)	14/21	100¶	1/21 (5)	—	No HIV
Reinus 1992 (USA)	23/24	70	0/16	0/8	0/4 (0)
Total	1317/1640	54[3] (648/1204)	56/903 (6.2; 95% CI 4.6% to 7.8%)	0/735 (0.0; 95% CI 0.0% to 0.4%)	28/177 (15.8; 95% CI 11.8% to 19.8%)

* Retrospective analyses of children born after infection of mothers with hepatitis C from anti-D immunoglobulin.
† Estimated number from proportion positive by polymerase chain reaction (46%) in total cohort infected from anti-D immunoglobulin.
‡ Number of mothers corresponding to these 55 perinatally exposed children (subgroup of tested children) not known and may be less than 55.
§ Transmission case from HIV positive mother of unknown status of hepatitis C by polymerase chain reaction.
¶ Only mothers with evidence of chronic hepatitis C infection selected.
[1] Hepatitis C RNA determination performed on only 37/70 mothers in study.
[2] Retrospective study with hepatitis C diagnosis of mothers from stored serum samples taken for regular monitoring of HIV status with subsequent hepatitis C testing of children born after date of mother's infection.
[3] Excludes studies where only mothers with chronic hepatitis C infection selected.

Table 2 Studies on transmission of hepatitis C through transplant and blood transfusion with information on hepatitis C status by polymerase chain reaction in source cases

Study	No of subjects	Source positive by polymerase chain reaction (%)	Transmission of hepatitis C (proportion (%))	
			Positive by polymerase chain reaction	Negative by polymerase chain reaction
Vrielink 1995 (Holland)*	71/94 (blood donor/recipients)	31	26/32 (81)	0/62†
Foberg 1996 (Sweden)*	12/36 (blood donor/recipients)	75	21/27 (78)	0/9
Norda 1995 (Sweden)*	21/39 (blood donor/recipients)	33	11/11 (100)	0/26‡
Shuhart 1994 (USA)	12/12 (bone marrow donor/recipients)	58	7/7 (100)	0/5
Periera 1992 (USA)	11/16 (organ (heart, liver, kidney) donor/recipients)	82	13/13 (100)	0/3
Roth 1992 (USA)	21 kidney transplant recipients	33	1/7 (14)	0/14
Total	148/218	41	83/97 (85.6; 95% CI 78.6% to 92.6%)	0/119 (0.0; 95% CI 0.0% to 2.5%)

* Retrospective studies of donors positive for antibody to hepatitis C and their multiple recipients of blood component.
† Excludes those who received ELISA positive (first generation), RIBA negative blood (n=78) as probable false positive ELISA results.
‡ Two recipient cases excluded: one recipient found to be positive for antibody to hepatitis C and positive by polymerase chain reaction but had received over 100 blood components from donors of unknown hepatitis C status (two other recipients from same donor negative by polymerase chain reaction had no evidence of infection). Further recipient was ELISA positive but negative by polymerase chain reaction and had also received previous blood components from donors of unknown hepatitis C status.

body to recipients negative for hepatitis C (table 2) gave a pooled transmission rate of 78% (72% to 94%) from donors positive by polymerase chain reaction compared with 0% (0% to 15%) from donors negative by polymerase chain reaction.[32-34] Three retrospective studies of transmission after transfusion of blood components from donors positive for hepatitis C antibodies demonstrated a pooled transmission rate of 83% (74% to 92%) from donors positive by polymerase chain reaction compared with no definite case of transmission among 97 recipients of blood components from negative donors.[35-37] One study found two recipients of blood component from donors negative by polymerase chain reaction to be positive for hepatitis C antibody (one negative by polymerase chain reaction, one positive), but pre-existing infection with hepatitis C could not be excluded as they had received multiple previous transfusions. Furthermore, the donor negative by polymerase chain reaction who corresponded to the recipient who was positive for hepatitis C antibody and positive by polymerase chain reaction had two further recipients who underwent testing, both of whom had no evidence of hepatitis C infection.

Although several studies have examined prevalence and incidence of hepatitis C among healthcare workers, only two studies have reported on hepatitis C antibodies and hepatitis C polymerase chain reaction status in source cases of needlestick exposures to healthcare workers (table 3).[38 39] With combination of the results of these two studies, the transmission rates for hepatitis C after needlestick exposure to patients positive for hepatitis C antibody was 6.1% (2.3% to 9.9%) from patients positive by polymerase chain reaction and 0% (0.0% to 18.5%) after exposure to those negative by polymerase chain reaction.

Discussion

The absence of hepatitis C viraemia detectable by polymerase chain reaction seems to indicate an extremely low risk of transmission. In the 29 studies examined, a total of 874 people were exposed to sources positive for hepatitis C antibodies but negative by polymerase chain reaction through vertical, transplant, blood component transfusion, and needlestick exposures. Among these people no definite case of transmission was reported. In contrast, 148 cases of transmission occurred among the 1148 people exposed to sources positive for hepatitis C by polymerase chain reaction. Pooled rates of transmission from such sources were 6.2% after perinatal exposure, 6.1% after needlestick exposure, 78% after transplant exposure, and 83% after transfusion of blood components.

On the basis of vertical transmission studies, level of hepatitis C viraemia and coinfection with HIV are also risk factors for transmission. For mothers positive for antibody to hepatitis C and HIV perinatal transmission occurred in 16% of cases, while the rate of transmission from those seronegative for HIV or of unknown status was less than 2%.

A potential limitation in the estimation of hepatitis C transmission rates is the process of weighting studies according to sample size, with a single large study such as the cohort of women infected with contaminated anti-D immunoglobulin described by Power et al having a large influence on the pooled estimate of vertical transmission. If both retrospective studies of mothers infected with contaminated anti-D immunoglobulin[22 23] are excluded, the pooled vertical transmission rate from mothers positive for hepatitis C

Table 3 Studies on transmission of hepatitis C by needlestick exposure with information on hepatitis C status by polymerase chain reaction in source cases

Study	No of subjects	Source positive by polymerase chain reaction (%)	Transmission of hepatitis C (proportion (%))	
			Positive by polymerase chain reaction	Negative by polymerase chain reaction
Mitsui 1992 (Japan)	74	92	7/68 (10)	0/8
Sodeyama 1993 (Japan)	90	89	2/80 (2.5)	0/10
Total	164	90	9/148 (6.1; 95% CI 2.2% to 10.0%)	0/18 (0; 95% CI 0.0% to 15.3%)

by polymerase chain reaction increases from 6.2% to 9.7%.

A recent editorial highlighted the importance of individual characteristics associated with an increased likelihood of transmitting hepatitis C in various settings.[40] It also asserted, however, that advice to patients with hepatitis C on their infectiousness could not be based on polymerase chain reaction testing for detection of hepatitis C viraemia. The possibility of both false positive and false negative results,[41] the difficulty of interpretation of results, and the lack of widespread availability of polymerase chain reaction testing were put forward as supportive arguments. A particular concern was that a person with very low level viraemia could still transmit hepatitis C if the inoculum was large enough.

Advances in technology

Rapid developments in polymerase chain reaction technology, however, have overcome many of these concerns. The sensitivity has been optimised through the use of nested primers based on the very highly conserved 5' non-coding region of the hepatitis C genome.[42] Thus, improved standardisation of technology in conjunction with ongoing monitoring by national reference laboratories should limit the possibility of false negative results. The findings from our review also support the high sensitivity of hepatitis C polymerase chain reaction, at least in the setting of research laboratories, where specimens were generally tested in duplicate.

The main drawback of extreme sensitivity of polymerase chain reaction technology is an enhanced possibility of contamination and thus suboptimal specificity. This has been emphasised by an international quality assurance survey which detected false positive results from a large number of laboratories.[43] Although increased vigilance to limit contamination and continued monitoring of specificity of the reaction are required, an occasional false positive result does not affect the finding of absent transmission of hepatitis C from patients negative for hepatitis C by polymerase chain reaction and the implications arising from such a finding.

The labour intensiveness of in house polymerase chain reaction technology, in particular nested reaction, has limited its availability. New methods such as nucleic acid amplification system (NASBA) and the Amplicor kit (Roche Diagnostic Systems, Basle, Switzerland), however, enable testing of large numbers of specimens in a single day and have equal sensitivity and specificity to the in house methods.[44]

Our review of published studies of hepatitis C transmission strongly supports the use of polymerase chain reaction testing for determination of infectiousness among people positive for hepatitis C antibodies. Even in situations where the hepatitis C inoculum was large, such as after blood transfusion, no definite case of transmission from a person positive for hepatitis C antibody but negative by polymerase chain reaction was documented.[35-37]

Implications for advice

Despite the improvements in polymerase chain reaction technology we have outlined, we would recommend that a person with hepatitis C is

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Key messages

- Between 20% and 50% of people infected with hepatitis C virus do not progress to chronic infection

- Polymerase chain reaction can detect ongoing hepatitis C viraemia and thus the presence of chronic infection

- The risk of transmission from people who are positive for hepatitis C antibody but have negative results by polymerase chain reaction is extremely low

- The rate of transmission from people who are positive for hepatitis C antibody and have positive results by polymerase chain reaction varies from 6% for mother to child transmission and occupational exposure to about 80% after transplantation or transfusion of blood components

- Polymerase chain reaction should be used to define infectiousness among people who are positive for antibodies to hepatitis C

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counselled on the basis of a persistently positive or negative hepatitis C polymerase chain reaction (at least two tests over a three month period) rather than a single assessment of polymerase chain reaction status. Even greater consistency would be required in a person receiving or having received interferon treatment because of the fluctuation in hepatitis C polymerase chain reaction status among this group. The greatest benefit would be in identifying those people with antibody to hepatitis C who have no biochemical or clinical evidence of chronic infection and who are persistently negative by polymerase chain reaction. This group of people could be counselled as to their non-infectiousness and most probable lack of chronic hepatitis C infection, with polymerase chain reaction having a similar role to that of hepatitis B virus core antigen in defining infectiousness and hepatitis B virus surface antigen in defining chronic infection.

Pregnant women, or women considering pregnancy, who are positive for hepatitis C antibody could be offered polymerase chain reaction testing to assist in determining their risk of transmitting hepatitis C to their infants; a woman persistently negative by polymerase chain reaction could be reassured that her risk of transmitting hepatitis C perinatally was essentially nil.

Determination of hepatitis C polymerase chain reaction status would also be useful after a needlestick exposure to blood or body fluid from a patient positive for hepatitis C antibody. If the source patient had no biochemical or clinical evidence of chronic hepatitis C infection and was negative by polymerase chain reaction, an exposed healthcare worker could be informed that the risk of acquiring hepatitis C was negligible. This information could allay considerable anxiety over the required 6-9 months before tests for hepatitis C are concluded.

The recent reports of hepatitis C transmission from two cardiothoracic surgeons to their patients has

placed increased scrutiny on healthcare workers who are positive for hepatitis C antibody.[45][46] In some places surgeons are already prevented from performing procedures likely to risk exposure if they are found to be infected.[45] Hepatitis C polymerase chain reaction testing could be used to assess the potential for transmission from infected healthcare workers. While surgeons positive by polymerase chain reaction should be advised not to perform procedures that may lead to exposure, those surgeons who are persistently negative by polymerase chain reaction should not be required to undertake additional infection control measures.

Although transmission efficiency through sexual contact seems to be low, many people positive for hepatitis C antibodies are counselled to use condoms. A person found to be persistently negative by polymerase chain reaction could be advised that the risk of transmitting hepatitis C sexually was essentially nil.

Conclusions

In summary, it seems that there is virtually no risk of hepatitis C transmission in the absence of viraemia as detected by polymerase chain reaction. This finding has important implications with regard to counselling both those people at risk of transmitting hepatitis C and those exposed to infective sources. Additional investigation of transmission based on clinical stage of infection, level of viraemia, and genotype is required to define the level of infectivity further in various settings.

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Evaluation of validity of British anthropometric reference data for assessing nutritional state of elderly people in Edinburgh: cross sectional study

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Abstract

Objectives: To evaluate the appropriateness of two sets of commonly used anthropometric reference data for nutritional assessment of elderly people.

Design: Cross sectional study.

Setting: Two general practices in Edinburgh.

Subjects: 200 independently living men and women aged 75 or over randomly recruited from the age and sex register of the practices.

Main outcome measures: Weight (kg), knee height (cm), demispan (cm), mid-upper arm circumference (cm), triceps skinfold thickness (mm), arm muscle circumference (cm) body mass index (kg/m²), and demiquet (kg/m²) in men and mindex (kg/m) in women.

Results: Men and women in Edinburgh were significantly shorter than those in measured for the Nottingham reference data (demispan 0.79 *v* 0.80 (P < 0.05) for men and 0.72 *v* 0.73 (P < 0.01) for women). Comparison with data from South Wales showed that men and women from Edinburgh had significantly greater mid-upper arm circumference, triceps skinfold thickness, and arm muscle circumference. No one fell below the 10th centile of the South Wales data (the commonly used cut off point for determining malnutrition) for these measures.

Conclusions: Both sets of reference data commonly used in Britain may be inappropriate for nutritional screening of elderly people in Edinburgh. Contemporary reference data appropriate for the whole of Britain need to be developed, and in the longer term biologically or clinically defined criteria for undernutrition should be established.

Introduction

Malnutrition is common, serious, and largely unrecognised in British hospitals.[1] It is also particularly common in old age.[2,3] Good anthropometric reference data are therefore fundamental in assessing the nutritional state of elderly people as well as in studies quantifying the prevalence of malnutrition and screening for malnourished people. However, there are few anthropometric data from large representative samples of elderly people,[4] and geographical variation in anthropometric variables might be large.[5]

Two sets of anthropometric reference data are widely used in nutritional assessment of elderly people in Britain. The first set is data from Nottingham on weight, demispan, demiquet (weight/demispan²) for men and mindex (weight/demispan) for women.[6] These data were obtained in the 1980s from a representative sample of 890 people aged 65 or over who were not living in institutions and have been suggested for use to identify people at extremes of the dis-

tribution.[7] The second set comprises data on body mass index, mid-upper arm circumference, triceps skinfold thickness, and arm muscle circumference collected from a broadly representative sample of about 1500 elderly subjects living in South Wales in the 1970s (7% in institutions).[8] We conducted a study to evaluate the appropriateness of these anthropometric data in nutritional assessment of a representative sample of elderly people living in Edinburgh.

Subjects and methods

We randomly selected a sample of men and women aged 75 or over who were living independently and registered with two general practices in Edinburgh. We used a quasi-random sampling frame in which we contacted every nth eligible patient from the age-sex registers. The patients were taking part in a larger study of potential risk factors for poor nutritional state in people over 75. For that study it was calculated that if the true correlation between any two variables was 0.2, a sample size of 200 would give an 80% chance of detecting the association as significant at the 95% significance level (P = 0.05). Assuming a 35% non-response rate, about 300 people would need to be asked to join the study.

We sent out a total of 246 contact letters to potential subjects. Two hundred people were recruited to the main study, giving a response rate of 81%. Seventeen patients declined to take part in the study, including having a terminal illness (n = 4), looking after an ill partner (n = 3), or being in the process of moving into a nursing home, long stay ward, or residential accommodation (n = 10); 23 people withheld their consent and six did not reply to the contact letter.

All measurements were performed in the subject's own home in an attempt to improve the recruitment and participation rates. Written informed consent was obtained before measurements were made, and the study was approved by Lothian Health Board ethics committee.

Each subject was weighed on calibrated portable scales to the nearest 0.5 kg without shoes but in indoor clothing, which was then accounted for. Any extreme signs of oedema were noted, and any subjects affected were excluded from weight calculations.

The simplest form of nutritional assessment is where weight is adjusted for height. However, because of the problems of spinal curvature and kyphosis that occur with advancing age, we used two standard alternative approaches for estimating height—demispan and knee height. Demispan is the distance from the web between the third and fourth fingers along the outstretched arm to the sternal notch with the arm in the corneal plane. It was measured on the left arm unless it had been affected by disease or disability by using a plastic tape measure which had a button

attached to anchor it at the base of the subject's fingers.[9] Measurements were made to the nearest 10 mm. Knee height measurements were made with the Ross knee height calliper, which has been shown to have acceptable accuracy and reliability.[10] The left leg was measured with the subject supine unless it had been affected by disease or disability.[11] Measurements were made to the nearest 1 mm, and body height was estimated by using the equations produced by Chumlea et al.[11]

We calculated body mass index (kg/m²) using the stature estimated from the knee height measurement. This procedure produces unbiased estimates of stature for groups.[12] We also calculated mindex (weight/demispan (kg/m)) for women and demiquet (weight/demispan² (kg/m²)) for men.[6]

Measurements of the upper arm were made on the left arm unless it had been affected by disease or disability. We measured mid-upper arm circumference to the nearest 1 mm with a plastic tape measure and triceps skinfold thickness with calibrated Holtain skinfold callipers to the nearest 0.2 mm using standard techniques.[13] Arm muscle circumference and corrected arm muscle area were calculated from these measurements[14]: arm muscle circumference (cm) = mid-upper arm circumference (cm) − (triceps skinfold thickness (mm) × π). Corrected arm muscle area (cm²) = (arm muscle circumference (cm)²/4π) − 10 (for men) or (arm muscle circumference (cm)²/4π) − 6.5 (for women).

Additional social information, including the subject's postcode, was collected to determine the extent to which the sample was representative of the population from which it was drawn. Analysis was carried out using the Scottish ACORN (a classification of residential neighbourhoods) classification system, which is formulated from information on over 100 variables collected from the 1991 census data. Socioeconomic classification in the system is based on factors such as home ownership, age, health, employment, and occupation as well as special factors such as floor of residence and overcrowding. The classification is divided into 43 types that make up eight groups. Because of our relatively small sample size we restricted the classification to the group level.

Two sample unpaired *t* tests were used to investigate any significant difference between the Edinburgh data and those in the reference data from Nottingham[6] and South Wales.[8] Standard deviations were not available for the South Wales data and we therefore used the Edinburgh standard deviations in the analysis. The Kolmogorov-Smirnov goodness of fit test was used to ascertain that the data were normally distributed for each parameter.
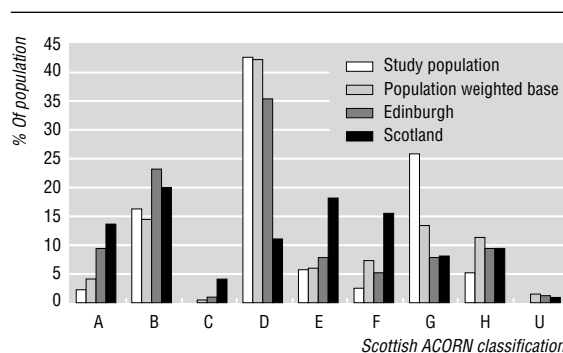
Fig 1 Socioeconomic classification by ACORN system of 200 people aged 75 years or over who were living independently in Edinburgh compared with classification for weighted population base and for total populations of Edinburgh and Scotland

Results

The sample was broadly representative of Edinburgh in terms of socioeconomic characteristics (fig 1). The mean (SD) age of non-participants (81.6 (4.9) years, range 75-95) was similar to the age of those who did participate (80.4 (4.9) years). The ratio of men to women was 62:138.

We obtained weight measurements from 188 (94%) subjects (59 men, 129 women), demispan and knee height from 189 (95%; 59 men, 130 women), and upper arm anthropometric data from 185 (92.5%; 59 men, 126 women). The distribution of each parameter was not significantly different from the normal distribution.

Men and women in Edinburgh were significantly shorter than those in Nottingham (0.79 m *v* 0.72 m, P<0.05 and 0.8 m *v* 0.73 m, P<0.01 respectively). In addition, table 1 shows that demiquet was significantly greater among men in Edinburgh than Nottingham (P<0.01).

Mid-upper arm circumference, triceps skinfold thickness, and arm muscle circumference were significantly greater in Edinburgh than in Wales for men and women of all ages (table 2). Body mass index was not significantly different for women in the two groups but was significantly greater in Edinburgh men aged 75-79 years (P<0.001) and 80-84 years (P<0.01) than for men in Nottingham.

Discussion

This study highlights significant differences in several important anthropometric indices of nutritional state between three large, broadly representative samples of elderly people from different regions in Britain

Table 1 Comparison of mean (SD) weight, demispan, demiquet, and mindex of men and women in Edinburgh with Nottingham reference data[6]

	Men			Women		
	Edinburgh (n=59)	Nottingham (n=153)	95% CI for difference in means	Edinburgh (n=129)	Nottingham (n=275)	95% CI for difference in means
Weight (kg)	71.5 (10.7)	68.6 (11.4)	−0.5 to 6.3	60.6 (11.9)	59.7 (11.6)	−1.6 to 3.4
Demispan (m)	0.79 (0.03)*	0.8 (0.04)	−0.03 to −0.0	0.72 (0.03)**	0.73 (0.04)	−0.02 to 0.0
Demiquet (kg/m²)	113.4 (16.9)**	106.0 (15.1)	2.7 to 12.1	—	—	—
Mindex (kg/m)	—	—	—	84.7 (15.4)	82.1 (15.2)	−0.6 to 5.8

*P<0.05, **P<0.01.

Table 2 Mean (SD) body mass index, mid-upper arm circumference, triceps skinfold thickness, and arm muscle circumference according to age for men and women in Edinburgh compared with reference data from South Wales[8]

	75-79 years			80-84 years			≥85 years		
	Edinburgh (n=31)	South Wales (n=119)	95% CI for difference between means	Edinburgh (n=18)	South Wales (n=56)	95% CI for difference between means	Edinburgh (n=10)	South Wales (n=31)	95% CI for difference between means
Men									
Body mass index (kg/m²)	26.4 (3.5)***	23.9 (n=188)	1.2 to 3.8	25.9 (2.6)**	23.7 (n=87)	0.8 to 3.5	24.5 (4.1)	23.1 (n=41)	−1.5 to 4.3
Mid-upper arm circumference (cm)	29.7 (3.2)***	24.9	3.5 to 6.1	29.2 (2.4)***	23.5	4.4 to 7.0	27.3 (3.9)***	22.1	2.3 to 8.1
Triceps skinfold thickness (mm)	11.4 (5.9)***	7.0	2.0 to 6.8	10.1 (3.2)***	6.6	1.8 to 5.2	9.5 (3.0)**	6.5	0.8 to 5.2
Arm muscle circumference (cm)	26.1 (2.7)***	22.1	2.9 to 5.1	26.0 (2.0)***	21.5	3.4 to 5.6	25.4 (4.2)**	20.8	1.5 to 7.7
Women									
Body mass index (kg/m²)	26.2 (4.7)	26.1 (n=329)	−1.1 to 1.3	26.8 (4.6)	25.5 (n=200)	−0.4 to 3.0	24.9 (3.8)	23.6 (n=88)	−0.3 to 2.9
Mid-upper arm circumference (cm)	29.9 (4.1)***	24.9	3.9 to 6.1	30.1 (3.9)***	23.5	5.1 to 8.1	27.9 (2.9)***	22.1	4.6 to 7.0
Triceps skinfold thickness (mm)	17.1 (5.5)***	14.6	1.0 to 4.0	17.9 (5.3)***	12.7	3.1 to 7.3	14.0 (3.4)***	11.5	1.0 to 4.0
Arm muscle circumference (cm)	24.5 (2.9)***	20.0	3.7 to 5.3	24.5 (2.7)***	19.2	4.2 to 6.4	23.5 (2.1)***	18.2	4.4 to 6.2

*P<0.05, **P<0.01, ***P<0.001.

sampled at different times. These differences would be clinically important when deciding if an elderly person was malnourished and have a substantial impact on outcomes of screening for malnourished elderly patients or on estimates of the prevalence of malnutrition in research and clinical audit.

If the fifth (or even 10th) centile for mid-upper arm circumference, triceps skinfold thickness, or arm muscle circumference from the South Wales data were used as cut offs for malnutrition (as is common[1 3]) in our Edinburgh sample no men or women would fall below them. No Edinburgh men aged 80 years or over had a body mass index below the 10th centile. For arm muscle circumference and mid-upper arm circumference no men aged 75-9 were below the 25th centile and no older men were below the 50th centile. Furthermore none of our subjects had a corrected arm muscle area below the suggested cut offs of 16.0 cm² for men and 16.9 cm² for women. This measure is widely used as a simple index of undernutrition in old age.[14]

Comparison with the South Wales data suggests that no one in our population was undernourished. Although differences may exist in the prevalence of undernutrition in elderly populations throughout Britain, it seems unlikely that such large discrepancies can be explained by this. The differences are more convincingly explained by a shift in distribution of anthropometric data in Edinburgh compared with current British reference data.

Similar discrepancies with the current anthropometric reference data have been described for infants[15 16] and also in younger adults.[17] Furthermore,

the difference observed in skeletal size between people in Edinburgh and Nottingham, as shown by comparison of demispan measurements, is supported by data from a national survey of British adults.[18] French anthropometric data are very different from British data, and substantial geographical variation has been suggested to occur within France.[5]

In conclusion, simple anthropometric measurements can provide practical and valid indices of nutritional status.[1 19] It is important to assess nutritional state, especially in elderly patients because they are at high risk of malnutrition.[20] However, our study suggests that existing reference data for anthropometric nutritional assessment of elderly people in Britain are not representative of all populations. The discrepancy may be due to geographical differences or secular trends. Urgent steps must be taken to establish the reason for the differences and to obtain contemporary reference data appropriate for the whole of Britain. This will ensure that people with malnutrition are reliably identified and enable early and appropriate intervention.

It may be preferable to use alternative criteria to assess nutritional state. One such criterion would be percentage body fat, with minimum and maximum values based on biological or clinical evidence.[21] However, developing such an approach will take time, and nutritional assessment is likely to rely on anthropometric data for the foreseeable future. Our results show the need to consider the limitations of reference data when carrying out nutritional assessments.

Key messages

- Anthropometric reference data for assessing the nutrition of elderly people in Britain are limited

- This Edinburgh population showed significant differences from the commonly used reference data in several anthropometric measures

- Existing anthropometric reference data could lead to significant biases when used for screening for undernutrition or determining prevalence of malnutrition

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Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study

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Abstract

Objective: To investigate whether the association between low birth weight and increased risk of developing impaired glucose tolerance, insulin resistance, hypertriglyceridaemia, and hypertension in middle age is apparent by the age of 20 in people born small for gestational age.

Design: Regional cohort study.

Setting: Maternity registry, Haguenau, France.

Subjects: 236 full term singleton babies born small for gestational age (birth weight or length, or both, below third centile) during 1971-8 and 281 with normal birth weight (between 25th and 75th centile). All subjects were contacted and evaluated at a mean (SD) age of 20.6 (2.1) years.

Main outcome measures: Adult height; concentrations of glucose, insulin, and proinsulin during an oral glucose tolerance test; lipid and fibrinogen concentrations; and blood pressure.

Results: After sex and target height were adjusted for, subjects who had been born small for gestational age were significantly shorter at age 20 than those with a normal birth weight (men 4.5 cm shorter (95% confidence interval 6.0 to 3.0 cm); women 3.94 cm shorter (5.2 to 2.7 cm)). After sex and body mass index were adjusted for, mean plasma glucose concentration 30 minutes after a glucose load, fasting insulin concentration (in women), and insulin and proinsulin concentrations 30 and 120 minutes after a glucose load were significantly higher in subjects who had been born small for gestational age than in those with a normal birth weight. Mean lipid and fibrinogen concentrations and blood pressure were not different between the two groups.

Conclusions: Intrauterine growth retardation has long term consequences such as reduced final height. Raised insulin and proinsulin concentrations are present in young adults born small for gestational age and could be markers of early changes in insulin sensitivity.

Introduction

Intrauterine growth retardation has long term consequences for postnatal growth and development. Affected infants are known to be at a higher than average risk of illness and death from several neonatal disorders.[1] Although most (85-90%) will catch up in height during the first two years of life,[2 3] some children will remain short in childhood and adulthood.[3-6] A recent population based study following babies born small for gestational age to adulthood showed that they had a sevenfold higher risk of being short than subjects who were not small for gestational age.[3]

Recent findings suggest that the associated conditions of hypertension, non-insulin dependent diabetes or insulin resistance, and dyslipidaemia are more common in adults who had an abnormally low birth weight.[7-10] Increased death rates from cardiovascular disease have also been reported.[11 12] These studies indicate that these metabolic disorders may originate from impaired growth and development during fetal life.[13-16] None of the studies, however, specifically investigated subjects born small for gestational age since length of gestation was not precisely known. We conducted a large population based study to examine the effect of intrauterine growth retardation on final height and metabolic variables in a cohort of young people.

Subjects and methods

We identified subjects for study from a population based registry of the metropolitan area of the city of Haguenau in France. This registry records information

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on all pregnancies, deliveries, and perinatal events in the area. Haguenau Maternity Hospital is the main maternity centre for this region of north east France, and the population is mainly white. The degree of ascertainment of the registry is greater than 80%.[17] We selected subjects born between 1971 and 1978. During this period 10 830 singleton babies were born in the maternity hospital and included in the registry.

The growth standards of the population of Haguenau are different from those of the population of France in general because of the large number of Germanic people, so our standards were local values for birth weight, height, and head circumference by gestational age and sex as derived from live births registered during 1971-85. Gestational age was determined from the date of the mother's last menstrual period and by physical examination during pregnancy, and it was confirmed by ultrasound measurements when available. We included all 452 singleton subjects who had been small for gestational age and born at term (≥37 weeks of gestation) during 1971-8. Being small for gestational age was defined as having a birth weight or length, or both, below the third centile of the local standard values. The control subjects were 451 singletons who had had a normal birth weight for gestational age (between 25th and 75th centile); they were selected from the register as the first person with an appropriate birth weight who was born immediately after a subject who was small for gestational age without any attempt to match for sex and gestational age.

Altogether we identified 903 subjects for the study; 16 subjects with aberrant measurements (normal birth weight of greater than 3000 g but extremely short birth length less than 35 cm) due to recording errors at birth were excluded. Of the remaining 887 subjects, 517 (58%) agreed to take part in the study, 236 of whom had been small for gestational age and 281 controls. Table 1 shows the reasons for non-participation. As expected, the number of deaths was significantly higher in the group that was small for gestational age (32 (15%) v 9 (5%); P = 0.002). The other causes for non-participation were equally distributed between the two groups. The proportion of women was greater among participants than non-participants (55% (285) v 47% (1881); P = 0.02).

Among the control subjects we found no difference between participants and non-participants in gestational age at birth, placental weight, birth weight, and length at birth. Among the subjects who had been small for gestational age, the only variable that was significantly different between participants and non-participants was mean birth length, which was significantly higher for the participants (47.0 (SD 2.1) cm v 46.2 (3.3) cm; P = 0.005). This was partly explained by the greater severity of intrauterine growth retardation among those who had died, their mean

length at birth being 45.7 (3.9) cm and mean birth weight 2260 (380) g.

Degree of intrauterine growth retardation was evaluated by expressing birth weight and length as a standard deviation score and correcting for gestational age and sex according to the local growth standards. To evaluate intrauterine nutritional state the ponderal index was calculated as the ratio of birth weight (g) to the cube of length at birth ((cm) × 100) corrected for gestational age according to the standard of Miller and Hassanein.[18] We divided subjects into two groups according to whether the ponderal index was less than or equal to the third centile or greater than the third centile.

We asked each subject's parents for their current height and weight, and 97% of them were measured in the same standardised way as their child. Target height was calculated from mid-parental heights adjusted for the sex of the child.[19]

Subjects who agreed to participate in the study attended the hospital for a morning, and we took blood samples for measurement of fasting lipid concentrations (total cholesterol, high density lipoprotein cholesterol, triglycerides, apolipoproteins A1 and B) and concentrations of fibrinogen, glucose, insulin, and proinsulin. Subjects also had an oral glucose tolerance test with a glucose load of 75 g, and further blood samples were taken after 30 and 120 minutes for measurement of plasma glucose and serum insulin and proinsulin concentrations. We obtained a medical history using a questionnaire. The prevalence of diabetes, hyperlipidaemia, and hypertension was assessed in subjects and their parents and did not differ between the two groups.

The height of all subjects was measured twice to the nearest 0.1 cm by one paediatrician using the same wall mounted stadiometer; the average value was used in the analysis. Weight was measured on portable scales to the nearest 0.1 kg, and weight for height was assessed as body mass index (weight (kg)/(height)^2 (m)). Waist circumference was measured at the level of the umbilicus and hip circumference was measured at the level of the greater trochanter.

We measured blood pressure in the right arm of seated subjects after five minutes' rest using an automated device (Dinamap, Critikon, Neuilly Plaisance, France) and a cuff of the recommended size for the mid-upper arm circumference. Three measurements were made at an interval of one minute, and the average of the last two measurements was used in the analysis.

Laboratory procedures

All blood samples except those for measurement of glucose, fibrinogen, and lipid concentrations were centrifuged and serum was stored at −20°C until assayed. Glucose (mmol/l), cholesterol (mmol/l), high density lipoprotein cholesterol (after precipitation by phosphotungstic acid and magnesium chloride), and triglyceride (mmol/l) concentrations were measured by enzymatic methods. Fibrinogen (g/l) was measured by an automated method based on the time of fibrin formation after addition of thromboplastin-calcium reagent. Apolipoprotein A1 (g/l) and apolipoprotein B (g/l) were measured by kinetic nephelometry using

Table 1 Reasons for non-participation in study

	Small for gestational age (n=216)	Appropriate for gestational age (n=170)	Total (n=386)
Incorrectly recorded birth measurement	16	0	16
Had died	32	9	41
Was adopted	5	5	10
Did not want to participate	88	103	191
Follow up details lost	75	53	128

specific antibodies to apolipoprotein A1 and B (Beckman, France).

Insulin concentration (pmol/l) was measured by a specific immunoradiometric assay using two monoclonal anti-insulin antibodies (Bi-insulin immunoradiometric assay, ERIA Diagnostics Pasteur, France). Intact proinsulin, split (32,33) proinsulin, and des (31,32) proinsulins did not cross react.[20]

Proinsulin concentration (pmol/l) was determined by an immunoradiometric assay based on a previously described method[21]; briefly, proinsulin was measured by using two monoclonal antibodies, one recognising the insulin part of the proinsulin molecule (3B1, Biochem Immunosystems, United Kingdom) and the other recognising the C peptide part (PEP-001, Novo Nordisk, France) of the proinsulin molecule. Molar cross reactivities of proinsulin intermediates were 80-100% compared with those of intact proinsulin. The detection limit was 0.3 pmol/l with an intra-assay coefficient of variation of less than 6% and an interassay variation of less than 9%.

Statistical analysis

Statistical analysis was performed with SAS software (SAS Institute, Cary, NC). Results are expressed as means (SD). Insulin, proinsulin, triglyceride, and apolipoprotein A1 concentrations had skewed distributions, which were normalised by logarithmic transformation.

One subject who was being treated for cystic fibrosis and diabetes, three who were being treated for hypertension, and four who were being treated for hyperlipidaemia were excluded from the analyses of glucose tolerance, blood pressure, and lipid concentrations respectively.

The significance of differences between groups was assessed by the χ^2 test, Fisher's exact test, and Student's t test as appropriate. A P value of 0.05 was considered to be significant.

Multiple linear regression models (GLM procedure) were fitted with biological parameters and blood pressure as dependent variables and group (small or appropriate for gestational age), sex, and body mass index as explanatory variables. First order interaction between groups and sex was tested. If significant, separate analyses were carried out for men and women. The relations between biological parameters and gestational age, adjusted for sex and body mass index, were investigated in separate linear models according to whether subjects had been small or of an appropriate size for gestational age, and a significant interaction was found between group and gestation. A stepwise multilinear regression was used to assess the relations between systolic blood pressure and biological parameters such as glycaemia and insulin, proinsulin, and lipid concentrations after adjustment for sex, body mass index, and family history of high blood pressure.

Multiple linear regression was also used to assess the relation between final height and group (small or appropriate for gestational age), adjusted for sex and target height.

The study protocol was reviewed and approved by the faculty ethics committee and all subjects and parents gave signed written consent.

Results

Anthropometric parameters

Table 2 shows the clinical characteristics at birth of the two study groups. No significant differences were found in age, sex distribution, and gestational age between the two groups. Among the subjects small for gestational age, birth weight was below the third centile in 128 (54%), birth length was below the third centile in 50 (21%), and both birth weight and length were below the third centile for 58 (25%) subjects. The birth weight was from 2 SDS (standard deviation scores) to 3 SDS below the mean and more than 3 SDS below the mean in 101 and 14 subjects, respectively. The birth length was from 2 SDS to 3 SDS below the mean and more than 3 SD below the mean in 81 and 30 subjects, respectively. Fifty six (24%) had had a ponderal index below the third centile at birth. Subjects who had been small for gestational age had the following risk factors for intrauterine growth retardation: pregnancy induced hypertension (63 subjects, 27%), maternal smoking during pregnancy (72, 32%), congenital abnormalities (28, 12%), and maternal short stature (22, 9%); some subjects had more than one factor.

The mean (SD) age of the population at the time of the study was 20.6 (2.1) years (range 16.6-24.5 years). As shown in table 3, the mean height, weight, and head circumference at the time of study were significantly lower in those who had been small for gestational age than in those born at normal birth weight. The mean body mass index and ratio of waist to hip measurements were similar in the two groups. As the mean height of men was significantly lower from 16.6 to 18 years than from 18 to 24.5 years, we assumed that some of the younger men had not achieved their final height and excluded those younger than 18 from analysis of final height (19 who had been small for gestational age and 21 controls). However, we included all the women as they had completed puberty, with menarche having occurred at least 18 months before the study. No significant difference was found in mean (SD) age at menarche between the two groups (12.6 (1.6) v 12.9 (1.7) years). The mean target height was lower in subjects who were small for gestational age but was significantly different only for women (P = 0.0001). Parents of subjects who had been small for gestational age were shorter than those of control subjects (P = 0.02 for paternal height, 172.3 (6.7) v 173.8 (6.4)

Table 2 Characteristics at birth of subjects who were small for gestational age or who had appropriate birth weight for gestational age. Values are means (SD) unless stated otherwise

	Small for gestational age (n = 236)	Appropriate for gestational age (n = 281)	P value
Gestational age (weeks)	39.7 (1.2)	39.9 (1.2)	0.11
Birth weight (g)	2550 (334)	3410 (216)	
Birth length (cm)	47 (2.1)	50.4 (0.8)	
Head circumference (cm)	32.9 (1.5)	34.7 (1.1)	0.0001
Ponderal index	2.5 (0.5)	2.7 (0.1)	0.0001
Placental weight (g)	523 (120)	629 (118)	0.0001
Sex (No (%)):			
Male	103 (44)	129 (46)	0.61
Female	133 (56)	152 (54)	
Target height (cm):			
Men	174 (4.5)	175 (4.7)	0.07
Women	160 (5.4)	162 (4.8)	0.0001

Table 3 Anthropometric data at mean age of 20.6 (2.1) years in population of subjects who were born small for gestational age or who had appropriate birth weight for gestational age, by sex. Values are means (SD)

	Small for gestational age		Appropriate for gestational age		P value	
	Men (n=103)	Women (n=133)	Men (n=129)	Women (n=152)	Men	Women
Age (years)	20.5 (2.2)	20.4 (2.0)	20.8 (2.1)	20.8 (2.1)	0.44	0.09
Height (cm)*	174.5 (6.7)	160.5 (6.3)	178.9 (6.3)	166.2 (6.0)	0.0001	0.0001
Target height (cm)*	174.1 (4.1)	159.6 (5.4)	174.7 (4.7)	162.3 (4.8)	0.26	0.0001
Weight (kg)	68.2 (13.2)	56.6 (10.2)	72.5 (12.6)	61.0 (12.5)	0.01	0.001
Body mass index (kg/m^2)	22.6 (4)	22.0 (3.7)	22.6 (3.7)	22.1 (4.2)	0.92	0.81
Head circumference (cm)	56.3 (1.8)	54.2 (1.5)	57.2 (1.5)	55.2 (1.4)	0.0001	0.0001
Waist:hip	0.87 (0.06)	0.79 (0.06)	0.86 (0.05)	0.79 (0.07)	0.06	0.72

*Excluding men younger than 18 years old (small for gestational age n = 217, normal birth weight n = 260).

cm, P = 0.0001 for maternal height 160.8 (6.2) v 163.1 (5.6) cm).

After adjustment for target height, a significant deficit in final height was found in those who were small for gestational age (men: − 4.50 (95% confidence interval − 6.0 to − 3.0) cm, women: − 3.94 (− 5.2 to − 2.7) cm). Twenty nine (13.4%) subjects who had been small for gestational age were short (>2 SD below mean height of controls) compared with seven (2.6%) of those who had had a normal birth weight.

Metabolic variables

Oral glucose tolerance test
Table 4 shows the results of oral glucose tolerance testing in the two groups. After sex and body mass index were adjusted for, fasting plasma glucose concentration, fasting serum insulin (for men), and proinsulin concentrations did not differ between the two groups. Among women, fasting serum insulin concentrations were significantly higher in those who had been small for gestational age than in controls.

Glucose concentrations 30 minutes after a glucose load and insulin and proinsulin concentrations 30 and 120 minutes afterwards were significantly higher in subjects who had been small for gestational age. After sex and body mass index were adjusted for, insulin and proinsulin concentrations at all studied times were negatively correlated with gestational age in the group that was small for gestational age but not in the control

group (regression coefficients were − 0.078 for fasting insulin (P = 0.009), − 0.093 for insulin at 30 minutes (P = 0.006), − 0.093 for insulin at 120 minutes (P = 0.03), − 0.063 for fasting proinsulin (P = 0.03), − 0.084 for proinsulin at 30 minutes (P = 0.007), and − 0.064 for proinsulin at 120 minutes (P = 0.05)). Consequently, the difference between the groups in serum insulin and proinsulin increased with decreasing length of gestation. This finding was independent of the degree of intrauterine growth retardation as measured by numbers of standard deviations below the mean birth weight or birth length or of the ponderal index at birth.

Neither the ratio of proinsulin to insulin concentrations nor the ratio of the 30 minute increment in insulin concentration to the 30 minute increment in glucose concentration after the oral glucose load, taken as indicators of insulin secretion,[22] [23] were different between the two groups.

No association was found between the significant results of the glucose tolerance test and the final height, the degree of intrauterine growth retardation at birth (2-3 SD below the mean and >3 SD below the mean), the ponderal index at birth (low or normal), or risk factors associated with intrauterine growth retardation during pregnancy in subjects born small for gestational age.

Blood pressure
The mean systolic and diastolic blood pressure values in subjects who had been small for gestational age were not significantly different from those in control subjects after adjustment for sex, body mass index, and height. The mean (SD) systolic and diastolic blood pressure values were respectively 124.4 (10.5) v 125.3 (10.3) mm Hg and 62.7 (8.3) v 64.8 (8.8) mmHg in men and 117.0 (9.9) v 115.3 (10.3) mm Hg and 63.4 (8.8) v 62.6 (8.1) mm Hg in women. No relation was found between blood pressure and either placental weight or gestational age.

Stepwise multiple regression analysis showed that factors positively associated with systolic blood pressure were body mass index (P = 0.0001), sex (P = 0.0001), age (P = 0.01), height (P = 0.01), tobacco consumption (P = 0.02), fasting plasma insulin concentration (P = 0.002), and total cholesterol concentration (P = 0.03).

Serum lipid and fibrinogen concentrations
After sex and body mass index were adjusted for no significant difference was found in serum lipid or

Table 4 Mean (SD) results of oral glucose tolerance test in subjects born small for gestational age and in those born at appropriate birth weight for gestational age studied at age 20.6 (2.1) years

	Small for gestational age	Appropriate birth weight for gestational age	P value
Glucose (mmol/l)			
0 min (n=501)	4.81 (0.43) n=227	4.74 (0.38) n=274	0.07
30 min (n=481)	7.87 (1.82)* n=217	7.55 (1.39) n=264	0.03
120 min (n=480)	5.42 (1.14) n=216	5.26 (1.0) n=264	0.12
Insulin (pmol/l)			
0 min (n=482)*			
Men	4.35 (1.93) n=99	4.37 (1.55) n=120	0.99†
Women	5.47 (1.64) n=120	4.57 (1.54) n=143	0.0004†
30 min (n=441)*	54.1 (1.82) n=192	43.8 (1.82) n=249	0.0002
120 min (n=448)*	25.7 (2.24) n=201	22.1 (2.11) n=247	0.02
Proinsulin (pmol/l)			
0 min (n=500)*	8.76 (1.69) n=227	8.23 (1.66) n=273	0.11
30 min (n=475)*	34.5 (1.72) n=214	30.7 (1.66) n=261	0.01
120 min (n=472)*	50.7 (1.76) n=213	40.9 (1.82) n=259	0.0001

*Geometric mean concentrations.
†The interaction between groups and sex was significant (P=0.03). The effect of having been small for gestational age was present only in women.

fibrinogen concentrations (adjusted also for tobacco consumption) between the two groups (table 5). Triglyceride concentrations were positively related to fasting insulin and proinsulin concentrations and to insulin and proinsulin concentrations at 30 and 120 minutes ($P < 0.001$). No relation was found between high density lipoprotein cholesterol, insulin, and proinsulin concentrations.

Discussion

Our study demonstrates that being born small for gestational age is associated with reduced final height and increased serum insulin and proinsulin concentrations with normal glucose tolerance in young adults. In common with other studies[3 4] we also found a significant reduction in parental height in subjects who had been small for gestational age; maternal height was more reduced than was paternal height, as short women are known to have a higher risk of babies with intrauterine growth retardation.[24] Mean final height in the group born small for gestational age remained significantly lower after adjustment for the target height in both sexes. Reduced mean final height (without correction for target height) has been observed in adolescents aged 16-18 who had been born at term but small for gestational age.[3-6] Subjects with a normal birth weight in our study were 4 cm taller than the target height in both sexes, documenting the upward secular drift in height.

Being small for gestational age has been defined according to birth weight or birth length, and different cut off points have been used such as two standard deviations below the mean or the third, fifth, or 10th centile.[24] When Karlberg and Albertsson-Wikland used two standard deviations below the mean birth length as the cut off point 7.9% of subjects who had been small for gestational age were more than two standard deviations below the mean in height at 18 years of age, and 6.4% of subjects were in this category when small for gestational age was defined in terms of birth weight.[3]

Several studies have reported the efficacy of growth hormone in promoting growth of short children who were born small for gestational age.[25 26] However, as treatment with growth hormone may be a risk factor for insulin resistance,[27] it could increase any insulin resistance present before puberty and induce glucose intolerance. Although no increase in insulin resistance was found in recent studies of glucose metabolism in short children treated with growth hormone, regardless of the cause of shortness,[25 26 28] children should be monitored during treatment.

Earlier studies on increased risks of insulin resistance, hypertension, and dyslipidaemia did not have good information on gestational age and therefore could not determine the effects of premature delivery or malnutrition on the results.[8 10 29] Nevertheless, these studies did show that low birth weight was associated with a higher risk of non-insulin dependent diabetes mellitus or impaired glucose tolerance.[7 9] In a biethnic population in San Antonio, Texas, low birth weight was an independent risk factor for insulin resistance.[10] More recently a study of 1333 men aged 50-60 who were born and living in Uppsala confirmed that reduced fetal growth is associated with insulin resistance and non-insulin dependent diabetes

Table 5 Mean (SD) serum lipid and fibrinogen concentrations in subjects aged 20.6 (2.1) years born small for gestational age and appropriate birth weight for gestational age

	Small for gestational age	Appropriate birth weight for gestational age	P value
Cholesterol (n = 502) (mmol/l)	5.13 (1.1)	5.0 (1.0)	0.22
High density lipoprotein cholesterol (n = 495) (mmol/l)	1.32 (0.4)	1.34 (0.4)	0.61
Triglycerides* (n = 502)(mmol/l)	1.14 (0.6)	1.08 (0.6)	0.35
Apolipoprotein A1*(n = 502)(g/l)	1.64 (0.4)	1.67 (0.4)	0.42
Apolipoprotein B (n = 501)(g/l)	0.95 (0.3)	0.91 (0.3)	0.09
Fibrinogen (n = 501)(g/l)	2.95 (0.7)	2.90 (0.7)	0.36

*Geometric mean concentrations.

mellitus and suggested a specific association with thinness at birth.[29] This relation seems to be mediated through insulin resistance rather than through β cell dysfunction.[29-31]

We investigated whether these abnormalities could be detected in young adults born small for gestational age. We found that, independent of current body mass index and sex, plasma glucose concentration 30 minutes after a glucose load, serum insulin concentrations 30 and 120 minutes after a load, and proinsulin concentrations 30 and 120 minutes after a load were significantly higher in subjects who had been small for gestational age compared with the controls; in women serum fasting insulin concentrations were also significantly higher. A weak association between birth weight and plasma glucose concentration 30 minutes after a load has also been reported in children and young adults.[32-34] Our study shows that metabolic abnormalities described in middle age, which seem to indicate insulin resistance as a responsible factor, are already present in 20 year olds born small for gestational age. Gestational age at birth influences insulin and proinsulin concentrations in subjects born small for gestational age, suggesting that a shorter length of gestation increases the association of reduced fetal growth with insulin resistance later in life.

An increased ratio of proinsulin to insulin concentrations and a decreased ratio of the 30 minute increment in insulin concentration to the 30 minute increment in glucose concentration after oral glucose load may reflect β cell malfunction.[22 23] However, no significant changes in these ratios were observed between subjects who had been small for gestational age and control subjects. People who are small for gestational age may therefore have only insulin resistance, with no defects in insulin secretion. This hypothesis is supported by the results of the insulin response to the intravenous glucose tolerance test, which did not correlate with birth weight or ponderal index at birth.[29-31]

Previous studies have shown that cardiovascular risk factors associated with insulin resistance such as raised blood pressure, high serum triglyceride concentrations, and low concentrations of high density lipoprotein cholesterol were more prevalent at 1 year old in babies born with a low birth weight or whose weight was low at 1 year.[8 10 15 16 35 36] Plasma fibrinogen concentration has also been shown to be independently associated with an increased rate of ischaemic heart disease and is also linked with growth in infancy.[37] However, we found no increase in risk factors for coronary heart disease in subjects who had been small

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Key messages

- An inverse relation between birth weight and increased risk of developing impaired glucose tolerance, insulin resistance, hypertriglyceridaemia, and hypertension (syndrome X) in middle age has been reported

- In this study reduced final height and raised serum insulin and proinsulin concentrations during oral glucose tolerance testing were found in young adults born small for gestational age compared with young adults with an appropriate birth weight for gestational age

- Reduced fetal growth was not associated with impaired glucose tolerance, higher blood pressure, or abnormalities in lipid and fibrinogen concentrations

- Further longitudinal studies are required to examine the risk of developing the other elements of syndrome X later in life

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for gestational age, and lipid abnormalities characteristic of the insulin resistance syndrome were not associated with low birth weight in a study carried out in Sweden.[29]

We found no association between being small for gestational age and blood pressure at age 20, although other studies have found such associations.[38] A large population study found that systolic and diastolic blood pressure in adults and children were related to birth weight[36-44] and that low birth weight was associated with increased blood pressure.[36-43] The association was particularly strong when low birth weight occurred in conjunction with increased placental weight.[41 45] The association between birth weight and blood pressure was attenuated by standardisation for gestational age both in children[46] and in adults,[36] and low birth weight (<2500 g) was not associated with increased systolic or diastolic blood pressure in adolescence.[44 47-49] Adjustment for insulin concentrations 60 minutes after an intravenous glucose tolerance test reduced the significance of the associations between blood pressure and birth weight in Swedish men aged 50, suggesting that abnormalities in insulin secretion may be one of the factors mediating the association.[36]

Hyperinsulinaemia is an independent risk factor for ischaemic heart disease,[50] and insulin resistance may occur in the absence of obesity or high blood pressure.[51] Populations such as ours offer a unique opportunity for describing the natural course of hyperinsulinaemia and its outcome, and follow up should help resolve the controversy over its causes.

We found that young adults born small for gestational age had hyperinsulinaemia but not hypertension or dyslipidaemia. Whether other elements of syndrome X were present or will develop later requires further longitudinal study. Finally, insulin resistance should be documented by other more direct techniques. If it is present at a young age steps could be taken to prevent the development of non-insulin dependent diabetes—for example, by preventing obesity.

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Survey of occupancy of paediatric intensive care units by children who are dependent on ventilators

James Fraser, Quen Mok, Robert Tasker

Children dependent on ventilators who are being treated in paediatric intensive care units in the United Kingdom present a dilemma[1] because there is a shortage of appropriately staffed beds for emergency admissions.[2] The hypothesis that more admissions could be accommodated prompted a survey to assess the number of children chronically dependent on ventilators occupying these beds and to calculate the potential number of extra admissions that could occur should these beds become available.

Methods and results

In February 1996 we sent a questionnaire to the medical directors of all 24 paediatric intensive care units in England and Scotland; Wales did not have a paediatric intensive care unit recognised by the NHS executive. We obtained a 100% response rate with follow up questionnaires and telephone interviews. Chronic dependence on ventilation was defined as a failure to wean from mechanical respiratory support by three months after its initiation. We recorded the number of beds staffed, the number of admissions and refusals, and the number of patients dependent on ventilators from January to March 1996. We calculated the average length of stay per child in each unit using the number of bed days available to each unit (beds × days) and the number of children admitted. By then calculating the number of bed days taken up by each child dependent on a ventilator and by knowing the average

length of stay for each acute admission, we were able to calculate the number of potential extra admissions to each unit had the beds occupied by the children dependent on ventilators been available. The actual number is less than the potential number of extra admissions since only children who were refused admission could then be accepted into an available bed.

The 24 units surveyed provided a total of 191 beds, of which 152 were staffed. Eighteen children were dependent on ventilators in eight units, thus they occupied around 12% (18/152) of available beds. During the survey 267 children, including 143 children at the eight affected units, were refused admission. The potential spare bed capacity generated if the 18 beds used by the children dependent on ventilators had been available would have allowed for an extra 273 admissions. An additional 120 children could have been admitted to the eight affected units. The number of patients refused could therefore have been reduced from 267 (124 in units I-X plus 143 in units A-H) to 142 (124 in units I-X plus 23 in units A-H). This would have been a fivefold reduction from 143 to 23 patients in units A-H which translates to a total reduction in refusal rate of 45%, from 267 to 147 patients (table 1).

Comment

Children who are dependent on ventilators remain inappropriately in hospital for prolonged periods of

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Table 1 Potential reduction in refused admissions to paediatric intensive care units between January and March 1996 if bed days occupied by children who were chronically dependent on ventilators had been used for acute admissions

Units	Mean length of stay (days)	Chronic dependence on ventilators No of children	Chronic dependence on ventilators Potential No of available bed days	Potential No of extra admissions per month	Actual No of refusals (Jan+Feb+Mar)	Calculated extra admissions (Jan+Feb+Mar)	Calculated No of refusals
Units with children dependent on ventilators							
A	5	6	540	36	21+19+10=50	21+19+10=50	0
B	6	1	90	5	0+1+0=1	0+1+0=1	0
C	10	4	360	12	23+3+6=32	12+3+6=21	11
D	6	1	90	5	13+7+1=21	5+5+1=11	10
E	6	2	180	10	7+0+3=10	7+0+3=10	0
F	3.75	1	90	8	10+5+5=20	8+5+5=18	2
G	7	1	90	4	2+2+2=6	2+2+2=6	0
H	5.45	2	180	11	1+1+1=3	1+1+1=3	0
Total	NA	18	NA	273 in 3 months	77+38+28=143	56+36+28=120	23
Other units							
I-X	NA	0	NA	NA	124	NA	NA

NA=not applicable.

time and are occupying much needed acute paediatric intensive care unit beds.[3] The obstacles to discharging these patients fall into three categories: coordination of agencies, lack of institutional alternatives, and responsibility for funding. Coordinating the relevant agencies takes time, and early liaison is crucial once it becomes apparent that a child is dependent on a ventilator. If placement at home or in a local hospital is not possible, the availability of facilities such as community rehabilitation centres or hospital based long term ventilation units would allow intensive care beds to be released for emergency admissions. Which authority has financial responsibility for these children is unclear, and problems with funding delay discharge; health authorities need to accept that they are obliged to fund home care programmes, or money must be provided supraregionally.

During the winter months of January to March 1996, 12% of available beds in paediatric intensive care units were occupied by children dependent on ventilators. Alternative placements for these patients are needed urgently. Emergency admissions to these units were prevented because beds were occupied by children dependent on ventilators. With better prioritisation, the current number of beds is sufficient to accommodate a large proportion of acute admissions.

1 James I. Centralised paediatric intensive care beds are blocked. *BMJ* 1996;312:1476.
2 British Paediatric Association. *Report of a multidisciplinary working party on paediatric intensive care.* London: BPA, 1993.
3 De Witt PK, Jansen MT, Davidson Ward SL, Keens TG. Obstacles to discharge of ventilator-assisted children from the hospital to home. *Chest* 1993;103:1560-65.

Comparison of blood or urine testing by patients with newly diagnosed non-insulin dependent diabetes: patient survey after randomised crossover trial

Pat Miles, Joan Everett, June Murphy, David Kerr

Guidelines for the management of non-insulin dependent diabetes mellitus often contain little information as to which is the preferred method of monitoring glucose at home.[1] Although there is much enthusiasm for blood testing, previous studies have been inconclusive, probably reflecting the way patients were selected, as many have included people with poorly controlled, longstanding diabetes. Defects in patients' knowledge and diabetes education are likely to cause errors. Patients will also produce "dud results if their teachers are incompetent."[2]

We compared home testing of blood and urine in newly diagnosed patients with diabetes. All patients participated in an identical structured group education programme, beginning within a week of their diagnosis.

Subjects, methods, and results

In Bournemouth, patients with newly diagnosed diabetes are seen in groups of 6-16 in a nurse led group education session within a week of the diagnosis being made. Between December 1993 and December 1994 a total of 150 consecutive patients (91 men; average age 65 (range 31 to 91) years) were asked either to test once daily for glycosuria, alternating before or two

Table 1 Comparison of home testing of blood or urine by 150 patients with newly diagnosed diabetes. Differences are with first measurement of variable

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	Baseline	3 Months (crossover)		6 Months (own preferred method)		12 Months (own preferred method)*	
		Mean (SD)	Difference (95% CI)	Mean (SD)	Difference (95% CI)	Mean (SD)	Difference (95% CI)
No of subjects:							
Blood first	68	58		58		50	
Urine first	82	56		53		55	
Glycosylated haemoglobin (%):							
Blood first	10.3 (2.6)	8.8 (1.9)	−1.5 (−1.9 to −0.06)‡	7.8 (1.4)	−2.6 (−2.6 to −1.3)‡	7.5 (1.7)	−2.8 (−3.1 to −1.4)‡
Urine first	10.3 (2.3)	8.7 (1.7)	−1.6 (−2.3 to −0.8)‡	7.6 (1.4)	−2.7 (−3.1 to −1.5)‡	7.5 (1.2)	−2.8 (−3.3 to −2.0)‡
Body mass index (kg/m²):							
Blood first	26.5 (5.6)	26.6 (5.4)	1 (−0.9 to 0.2)	26.5 (5.5)	0 (−1.1 to 0.2)	26.5 (5.8)	0 (−1.1 to 0.3)
Urine first	28.0 (6.0)	27.9 (6.0)	−1 (−0.8 to 0.1)	27.5 (6.0)	−0.5 (−1.0 to 0.1)	27.8 (6.2)	−0.2 (−0.8 to 0.1)
Quality of life scores†:							
Blood first		49.5 (9.9)		50.8 (9.3)	1.3 (−0.5 to 3.4)	51.1 (8.7)	1.6 (−1.4 to 1.9)
Urine first		51.6 (11.5)		48.9 (13.0)	−2.7 (3.0 to 0.2)	51.7 (8.7)	0.1 (−1.4 to 1.9)

*Includes 11 patients who chose to use both methods.
†Scores similar to other groups of patients with stable diabetes.[3]
‡P<0.001 in comparison to baseline.

hours after different meals, or at bedtime (target aglycosuria), or to test capillary blood glucose once daily before a different meal, or at bedtime, each day (target <8 mmol/l). The allocation was altered from week to week.

One month later, patients attended the first of four structured education sessions where all aspects of treatment, including starting drugs, were supervised by the diabetes specialist nurses according to predetermined protocols. After three months, patients were crossed over to the other method of home testing. Individual monitoring techniques were checked after one and four months. After six months, patients continued with their preferred method for a final six months.

Over the initial three months, 36 patients dropped out; 10 were unwilling or unable to manage blood testing, eight were unwilling to continue with urinalysis or had an altered renal threshold for glucose, nine were lost to follow up or died, two had poor vision, and seven changed their minds about the study.

Glycosylated haemoglobin (non-diabetic value <6.5%), body mass index (weight (kg)/height (m)²), and wellbeing were compared between groups (table 1).[3] Patients compared methods for ease of use (70% (105) preferred urine testing and 15% (23) blood; 15% (22) were undecided), acceptability (44% (66) urine, 31% (47) blood), perceived accuracy (11% (17) urine, 76% (114) blood), and usefulness (21% (32) urine, 49% (74) blood).

At 6 months, 42% (63) opted for urine testing and 48% (72) for blood testing; 10% (15) chose both. Among the blood testers, 60% (43) were taking oral hypoglycaemics compared with 46% (29) of the urine testers.

Comment

For patients with longstanding diabetes, self monitoring of blood glucose does not necessarily improve glycaemic control nor facilitate weight reduction even when patients monitor accurately and compliance is excellent.[4] Here, only patients with non-insulin dependent diabetes of recent onset were studied, and the education programme was identical for all participants. Over 12 months, glycosylated haemoglobin concentrations fell to the same extent, without any adverse effect on quality of life scores, with both methods of self monitoring. After six months, roughly equal numbers of patients chose each method.

In clinical practice, it is often difficult for patients with non-insulin dependent diabetes to maintain multiple daily tests over any length of time. Our data show that multiple testing may not be necessary: glycosylated haemoglobin concentrations at 6 and 12 months were similar to those achieved in the intensively treated group of the diabetes control and complications trial, in which subjects (young patients with insulin dependent diabetes) tested blood glucose four or five times a day.[5]

For patients with newly diagnosed diabetes who are able or willing to self monitor blood or urine for glucose, both methods are equally efficacious in terms of achieved glycaemic control, acceptability to patients, and self management. In economic terms, however, urine testing costs about one sixth as much as blood testing.

1 Watkins PJ. Guidelines for good practice in the diagnosis and treatment of non-insulin dependent diabetes mellitus. *J R Coll Phys London* 1993; 27:259-66.
2 Tattersall R. Self monitoring of blood glucose concentrations by non-insulin dependent diabetic patients. *BMJ* 1992;305:1171-2.
3 Well-Being Questionnaire. In: Bradley C, ed. *Handbook of psychology and diabetes. A guide to psychological measurement in diabetes research and practice.* London: Harwood Academic, 1995:92.
4 Wings RR, Epstein LH, Norwalk MP, Scott N, Noeska R, Haggs S. Does self-monitoring of blood glucose levels improve dietary compliance for obese patients with type-2 diabetes? *Am J Med* 1986;81:830-5.
5 DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.

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Endpiece
Sydenham on therapeutic method

I watched what method Nature might take, with intention of subduing the symptoms by treading in her footsteps.

Thomas Sydenham (1624-89), *Medical observations*