
Chapter

IMMEDIATE AND LONG TERM SOMATIC EFFECTS AND HEALTH RELATED QUALITY OF LIFE OF BONE MARROW DONATION DURING EARLY CHILDHOOD. A SINGLE CENTRE REPORT IN 210 PEDIATRIC DONORS

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Abstract

The first successful European pediatric allogeneic bone marrow (BM) transplantation was performed in Leiden, the Netherlands, in 1968, with a 7-year old female sibling donor. Since then, more than 300 young children have donated BM in our unit. We first retrospectively studied a cohort of 210 donors, younger than 13 years at donation, to survey procedures of donor eligibility and reports on immediate effects of BM donation. We then performed a long-term follow-up (FU) and health related quality of life (HRQoL) study. Despite the occurrence of previous medical conditions, no child was declared unfit to donate. We found that iron deficiency anemia or low iron stores in BM did not result in treatment or extended FU. Harvest volumes exceeded 15 ml/kg in 65% of donors, with more than half requiring allogeneic blood transfusions. Donors had no structured FU after their first post donation control. In this study 25% of donors reported at least one somatic complaint at long term FU. Finally long-term HRQoL revealed high scores in most sub domains (representing a higher QoL), compared to norm groups. These results indicate the need for development of (inter) national guidelines for pediatric stem cell donor care management.

Background

In the Leiden University Medical Centre (LUMC), in 1968, the first pediatric stem cell donor donated bone marrow (BM) for the benefit of her baby brother. Since then in over 40 years, more than 300 children have donated BM. Pediatric stem cell donation poses an ethical dilemma in that it exposes a healthy child to a potentially harmful medical procedure that has no direct clinical benefit. This is counterpoised by the positive emotional impact of being able to help a seriously ill sibling[1]. BM donation in early childhood is rare, and as such, literature on immediate effects and long-term outcome is scant. Although no cumulative registry data is available, statistics provided by the CIBMTR show that in the year 2006 over 4000 patients under the age of 20 years underwent allogeneic transplant transplantation[2,3]. Approximately a third of these received a graft from a related donor. We would estimate this to equate to approximately 3000 pediatric donors recruited annually worldwide. BM donation by minors is, according to international legislation, restricted to siblings[4]. In contrast, living solid organ donation is in Europe not permitted under the age of 18[4,5], although in the Netherlands, every person over the age of 12 years is allowed to carry a donor codicil. The use of first cousins, although practiced, falls outside EU regulations. While in our institution the minimum age for donation is six months, harvests elsewhere from younger children have been described[6]. Even though BM donation is a generally accepted and legally permitted, young children are considered incapable of giving informed consent[7]. Informed consent procedures for children involved in BM donation have only lately been specifically addressed[5,8]. In most cases, however, parents or legal representative of the prospective donors will give proxy consent for BM harvest[1], leaving the donor no other choice but to donate[9]. The recognition that a legal representative is required to protect the interest of the young donor (under the law), has only recently been adopted[10], albeit not universally. Legal representation for the benefit of family donors has been suggested, although smaller centers might be less able to implement this policy[11-13]. The lack of formalized (long-term) follow-up (FU) programs for (pediatric) donors is making it even harder to study the outcomes and impact on health and health related quality of life (HRQoL) in large cohorts. With the introduction of the use of hematopoietic growth factors in healthy individuals, the call for FU programs has resulted in a recommended system for unrelated stem cell donors, carried out by donor registries[14]. Individual institutions are required to develop a (pediatric) donor care program at their own initiative.

In many countries transplantation centers (TC) are obliged to conform to an accreditation program such as the Joint Accreditation Committee ISCT & EBMT (JACIE) or the Foundation for the Accreditation of Cellular Therapy (FACT). These factors have led to demands for new guidelines for the care management of family donors. The current JACIE Standards (version 4) require written criteria for stem cell donation to protect the donors' safety, although there is no requirement for structured donor

follow-up at the present time[15]. In the 5th version, which will become actual in 2012, the section for donor selection, evaluation and management is extended, demanding TC's to develop a policy, including minor donors. So far, studies into donor experience and side effects have been undertaken in adult sibling donors where it was found that the physical side effects were outweighed by the reinforcement of donors' self esteem, and increased meaning and worth of life[16]. A Cochrane literature review focused on bone marrow versus peripheral blood stem cell donation in adult donors[17]. Since adverse events and complications in adult donors may differ from those in children, although the findings are of interest, they are not directly comparable. For child donors, literature on the immediate physical effects of donating stem cells is scant[6,18,19] or limited to the use of hematopoietic growth factors in children[20-25]. Furthermore research has concentrated more on the psychosocial effects in pediatric donors[9,26-28]. To date, no significant long-term FU studies in pediatric donors have been performed. We aimed to describe the characteristics of a large retrospective cohort of pediatric donors and further to analyze the immediate and long-term physical effects, medical outcome and HRQoL associated with the donation of BM in early childhood.

Donors & methods

Group I consisted of a retrospective analysis of recorded medical and/or computerized laboratory data. All donors aged less than 13 years at the time of donation, who donated BM from 1968-2002 (n=210), were eligible for this cross sectional study. Blood counts were expected to be performed during initial physical examination (PE), pre and post harvest. Datasets were obtained for medical history and examination, BM harvest volumes, immediate consequences of donation and erythrocyte transfusion history. Donor medical fitness and the immediate effects of the donation process were investigated. Bone marrow was harvested from the posterior iliac crests under general anesthesia. Red cells were salvaged from the graft and given back to the donor (institutional policy). According to our institutional guidelines, a target cell dose of 1-2 x 10^8/kg recipient body weight (BW) infused was aimed for successful engraftment. In cases where major ABO incompatibility was documented between donor and recipient, a minimum of 500 ml BM harvest was deemed necessary for processing. All available BM aspirates (n=145), routinely obtained at the time of harvest, were retrospectively analyzed to document hematological findings. A review of the original reports (produced by two independent observers) was undertaken by a trained pediatric hemato-morphologist, and representative archived material was evaluated to confirm the original findings. Furthermore the volume of BM harvested in relation to red cell transfusion requirements was investigated.

Group II consisted of a prospective cohort of childhood donors who were invited to complete a self reported questionnaire regarding general health and quality of life.

The inclusion criteria were at least 12 years of age at initiation of the study, resident in the Netherlands and fluency in the Dutch language. The invitation to participate consisted of a letter of explanation (consisting the background and objectives of the study) for donors and/or parents (in case the participant was younger than 18 years) and a request for informed consent. Surviving recipients and non-donor/non-patient siblings were invited to act as controls. The rationale to invite the survivors was to investigate whether their quality of life would impact the donors' responses

A self reporting health consumption questionnaire and validated questionnaires to assess HRQoL included Medical Outcomes Study Short Form-36, the General Health Questionnaire, and The Pediatric Quality of Life Inventory™ Version 4.0, depending on the age of the participant. Donors > 18 years (n=61) received the GHQ-12 and SF-36 questionnaires. The Medical Outcomes Study Short Form-36 (SF-36) is a widely used generic health status measure that is available as a validated tool in the Dutch language[29,30]. The SF-36 health survey is composed of 36 questions and standardized response choices. The instrument examines eight specific domains: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and general mental health (MH), scoring each on a scale of 0-100% (worst to best). Higher scores indicate a higher level of functioning or wellbeing.

The General Health Questionnaire (GHQ-12) has been extensively used as a short screening instrument for mental illness in general health care, and is available in the Dutch language. The instrument is found to be remarkably robust after widespread testing[31]. The instrument measures changes in normal psychological functioning. Items are rated on the standard 0-0-1-1 scale and summed to a total score.

The Pediatric Quality of Life Inventory™ Version 4.0 (PedsQL) is a modular instrument for measuring HRQOL in children and adolescents ages 2-18 years. The instrument consisting of four core scales (physical, emotional, social and school) was found to be valid and reliable[32]. All of the above, except for the physical functioning scale are summarized in the psychosocial health summery score. A five-point Likert scale is utilized and scores are linearly transformed to a 0-100 scale. The PedsQL™ 4.0 is applicable for healthy school and community populations, as well as pediatric populations with acute and chronic health conditions.

Where available, results were compared to Dutch norm groups (as provided with validated instruments) or information from the Dutch Central Bureau of Statistics (CBS)[33].

This study was approved by the Scientific Committee of the Willem Alexander Children's Hospital and the Committee for Medical Ethics of the LUMC in the Netherlands.

Statistical analysis

Descriptive analysis (e.g. histograms with normality curve, box plots), reported as percentages, mean values and standard deviations, was performed to examine whether the study groups were normally distributed. Analysis was performed using SPSS and MS Excel, to examine associations between the study groups. In addition patterns of association among variables were estimated based on variables' level of measurement. These included visual representation and statistical measures of association/difference (e.g. Chi-square, Fischer's exact test, paired T-test and analysis of variance (ANOVA)) to address the level of specificity. Differences and correlations were regarded as statistically significant if $p<0.05$.

Results

Group I - general

For 13 from the 210 eligible donors, no data was available, resulting in 197 donors (94%) eligible for further analysis. Two children included in the study were extended family donors (i.e. non-sibling relatives). They were cousins of the recipients and were HLA matched due to the presence of a frequently occurring haplotype in non consanguineous families. Donor characteristics of this group are summarized in Table 1.

Donor eligibility

All donors were evaluated as medically fit to donate by a qualified pediatrician, who until the early 1990's was a member of the pediatric transplant team, also involved in the care of the recipient. Thirteen donors in group I (7%) had a previous medical history; seven children had persistent problems at the time of physical examination (PE) prior to donation (Table 2), which warranted additional considerations. None were deemed unfit to donate. Only one child underwent physical evaluation prior to HLA typing.

Peri donation events

Of the seven donors with persistent problems at time of donation, four had documented severe adverse events during or immediately after harvest. Donor 027 was moderately difficult to intubate (Cormack and Lehane gr II: vocal cords

only partly visible) in light of an enlarged epiglottis, which was not documented at screening. Donor 071, a child with severe cardiac abnormalities, developed significant tachycardia during anesthetic, which responded to medical intervention.

Table 1: Demographic characteristics of donors

	All donors (n=210)	**Follow-up donors (n=79)**	
Donor characteristics	*at donation*	*at donation*	*at study*
Age in yrs. (median; range)			
Male	6.4 (0.6-12.0)	6.4 (0.6-11.1)	22.2 (12.8-39.4)
Female	7.7 (0.6-12.3)	7.1 (0.8-12.3)	23.9 (14.2-47.8)
Gender			
Male	113 (53%)	36 (45%)	
Female	97 (47%)	44 (55%)	
Recipient outcome			
1 year after donation	75% alive		78% alive
At time of study	60% alive		61% alive
Donor is (%)			
Twin sibling	4.3	3.6	
Younger sister	21.0	25.3	
Younger brother	24.3	22.7	
Older sister	23.3	30.8	
Older brother	26.2	16.4	
Younger cousin	0.9	1.2	
Ethnicity (%)			
Caucasian	80	87	
Recipient diagnosis			
Malignancy	139 (66%)	57 (72%)	
Immune deficiency	15 (7%)	3 (4%)	
BM failure	36 (17%)	13 (16%)	
Hemoglobinopathy	12 (6%)	4 (5%)	
Other	8 (4%)	2 (3%)	
Birth order (%) FU donors			recipients
Oldest child		33	36
Middle child		29	25
Youngest child		30	39
Only child (after bereavement)		8	n.a.

Table 2: Characteristics of donors with a pre-donation medical history

Gender (UPN)	Medical history	Age at donation	Harvest characteristics	Follow-up (self reported)
M (012)	Fontan procedure for hypoplastic heart; congenital asplenia*	8.4 yr	686 ml	Rulide prophylaxes; BMI 18
F (091)	Spastic tetraparesis due to perinatal asphyxia; suspicion for neurofibromatosis	7.7 yr	152 ml; Respiratory problems, one night ICU	Non responder
F	Blalock shunt for congenital transposition great arteries*	0.6 yr	No documentation	Non responder, recipient died
F (071)	Congenital heart condition, not other specified*	4.4 yr	681 ml; Tachycardia (Hb 6.4g/dl)	Stent placement; BMI 17
M	Premature born (34 weeks)	0.7 yr	131 ml	Non responder
M	Premature born (34 weeks)	8.9 yr	514 ml	Non responder, recipient died
F	Premature born (34 weeks); repeated febrile convulsions; pyelonephritis	6.5 yr	378 ml	Non responder
F	Premature born (36 weeks)	8.2 yr	748 ml; 2nd dx after 4 weeks for other sib	Non responder, 1st recipient died
F	Premature born (31 weeks); hypothyroidism*	1.7 yr	199 ml	Atopy; GE problems n.o.s.
M (027)	Non syndromal developmental delay*	7.8 yr	696 ml; Intubation gr II	Non responder, recipient died
M (081)	Failure to thrive*	0.7 yr	125 ml; Hypoxic, 50 ml FFP	Healthy
M	Heart murmur; testicular atrophy (suspicion adrogenital syndrom)	3.7 yr	396 ml	Non responder, recipient died
M	At 7 weeks: sleep apnea (6 months monitored)	5.6 yr	488 ml	Non responder

** indicates that the medical condition warranted consideration at time of donor physical examination. UPN of donors refer to the text*

Donor 091, a child with a severe tetraplegic handicap had post extubation breathing difficulties, leading to an overnight observation in the pediatric intensive care ward. Finally donor 081, a child of 7 months old with failure to thrive, weighing 8.3 kg, having undergone a harvest of 15 ml/kg bodyweight developed hemodynamic instability requiring volume replacement therapy with plasma. In spite of these operative complications, only one donor received donor FU.

Twelve of 210 (5.7%) donors donated sequentially: two donated to different recipients, the remainder donated for the same recipient due to either poor engraftment, rejection of the graft or relapse of the original disease. Median time between donations was 6.8 months (range 1-170 months). One child, who donated twice in four weeks for two recipients, was not re-assessed, but had laboratory results prior to the second donation; the other donors who donated more than once were all re-assessed for their second donation.

Three donors were diagnosed with minor infections pre-donation (sinusitis, otitis media) and treated with antibiotics; no FU was recorded.

Laboratory results

Laboratory results were available for 147/197 (74%) of donors. Both pre- and immediate post-harvest (within 24 hours) full blood counts were documented for 126 donors; nineteen donors had only pre harvest values documented. Older donors had a lower Hemoglobin (Hb) level pre donation than younger donors, possibly due to the harvest of an autologous unit. Despite transfusions, Hb levels after donation compared to pre donation, were reduced in 89% (n=113/147), with a median loss of 2.5 g/dl (SD 0,46; range 0.3-5.2; median Hb 10.5 g/dl; p=0.0001). In 28 donors a post donation Hb level lower than 9.7 g/dl (median 8.9 g/dl; range 6.6-9.5) was documented (p=0.0001). No medical intervention or laboratory FU was documented. These results are summarized in Table 3.

Table 3: Median Hb,Ht development at different stages of the donation process and harvest characteristics

	Physical examiniation Mean Hb/Ht levels		**Post donation (< 24 ht)**		**Hb loss**	**Paired T-test**	**95% CI**	**Median volume harvested**	
Age (yr)	**Hb Ht**	**N**	**Hb Ht**	**N**	**g/dl**	**P-value**		**ml/ kg BW (range)**	**Total volume (range)**
0-3	12.4 0.37	46	10.0 0.31	35	2.4	p<0.0001 p<0.0001	1.202-1.847 0.0487-0.0794	17 (7-47)	204 (115-799)
4-7	12.7 0.37	55	10.5 0.31	49	2.3	p<0.0001 p<0.0001	0.980-1.540 0.0415-0.0674	18 (6-44)	402 (128-794)
8-12	13.2 0.38	49	10.6 0.32	42	2.6	p<0.0001 p<0.0001	1.124-1.701 0.0505-0.0786	18 (9-31)	529 (299-1189)

Bone marrow analysis

BM reports from 145 donors were available. Seventy percent (n=106) bone marrow aspirates were representative for histological examination. Iron stores were determined by supra vital staining with potassium ferricyanide (Perls). Absence (n=16) or reduced (n=54) iron stores were evident, mostly in children with normal Hb levels. Age distribution analysis revealed that infants and pre pubertal children were more likely to have reduced BM iron stores. No further investigation into the iron status of the donors post harvest were undertaken and/or documented. Low iron stores of donors were not related to the transplant indication of the siblings (i.e. B-thalassemia, SAA). Four donors had decreased or absent megakaryocytes, but had normal peripheral platelet counts and morphology. Other documented abnormalities included white cell aberrations in 6%, mainly undiagnosed hypereosinophilia, lymphocytosis and five cases of mild leucopenia, none of which were actively pursued.

Harvest characteristics

Harvest volume data was available for 109 of all donations, including three second donations. Harvest volumes ranged between 6-47 ml/kg donor body weight (BW) (corrected for age, mean 18 ml[34], or 8-62% (mean 24%) of the estimated total circulating whole blood volume. In 65% (n=66) of donations the volume harvested exceeded 15 ml/kg donor BW, with 34 of these children donating more than 20 ml/kg. Donors with an older recipient (n=49) were more likely to donate a larger volume. In donors with a younger recipient (n=47), 21 donated more than 15 ml/kg, with six donating more than 20 ml/kg (see Figure 1). Transfusion data were available for 160 donors. Overall 94 donors (52.5%) received a blood transfusion, of which 74 were allogeneic. In children whose harvested volume exceeded 15 ml/kg donor BW, 71% (47/66) required blood transfusion (40 allogeneic, and 7 autologous stored units), compared to only 35% (14/40) donors when the volume was restricted to 15 ml/kg or less donor BW ($p<0.0005$). In total 25 children older than 10 yrs received their autologous red cells, harvested at the time of initial physical examination.

In 77 cases complete data regarding cell yield infused and total volume harvested were available. A poor cell yield in the graft (defined as $<1.0 \times 10^8$ per kg/recipient BW infused) was documented in only 10 cases, in all of whom greater than 15 ml/kg donor BW was harvested. None of these patients had documented graft failure, with eight long term survivors and two children having died from a relapse of their leukemia. A cell yield of $\geq 3.0 \times 10^8$ per kg/recipient BW was seen in 34 harvests; twenty of these donors donated more than 15 ml/kg donor BW. A major blood group incompatibility between donor and recipient requiring red cell depletion was evident in 18 couples, only six of whom were in the group of large volume harvests.

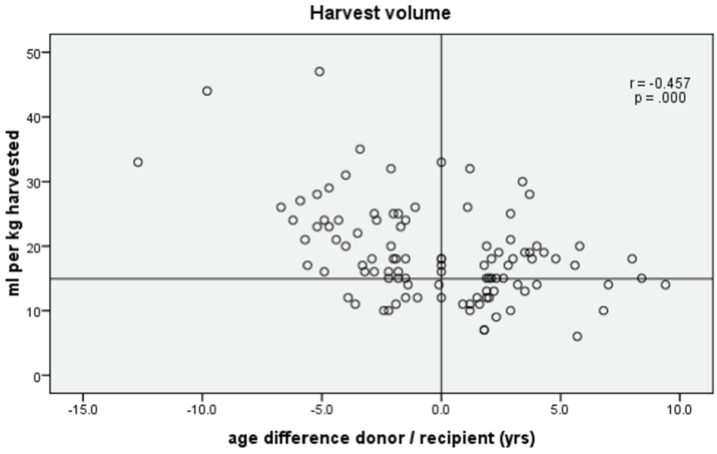

Figure 1: Harvest volumes often exceed 15 ml/kg (range 6-47 ml (mean 18 ml) donor BW, particularly in donors with an older recipient.

Short-term FU

Only 24 donors had documented FU information, within 100 days post donation, including hematological control. Only one donor (m, aged 7.9 yrs; Hb 9.0 g/dl, 1 week post donation) had a second FU 8 months after donation, due to persistent epistaxis. His Hb was 10.6 g/dl and platelet count 263 × 10^9/L at that time. With regards to the amount of donors that underwent large volume harvest and received allogeneic blood transfusions, no further FU with respect to the development of neither red cell antibodies nor transmissible diseases was performed. Reasons for not undertaking further evaluation for the remaining donors were not recorded.

Six donors had iron deficiency anemia pre-harvest, retrospectively diagnosed by characteristic red cell morphology in the presence of a hypochromic microcytic anemia in the absence of hemoglobinopathy. Intervention with iron suppletion was not documented. Full medical details were available for five of these donors. Four boys and one girl, aged between 3.1–11.4 years, who subsequently donated between 12 to 25 ml/kg body weight BM. Only three donors had their Hb levels controlled at six weeks FU, and in two donors persistent anemia was documented in the laboratory report. No data on long-term sequelae was available.

Self reported health questionnaire (group II); Long term FU

One hundred and ninety of the 197 group I donors were at least 12 years of age at the initiation of the study, and were thus eligible to participate. Seventeen of these were

referrals from abroad, with no known present address. The remaining 173 donors were invited by mail, to participate in a long-term FU study. Twenty-eight invitations were undeliverable, leaving 145 questionnaires that were presumed as received (Figure 2). Seventy-nine of 145 donors (54%) responded to the questionnaire, and were equally distributed throughout the study period when analyzed by five year intervals. Of 92 surviving transplanted siblings, 44 (48%) responded to the invitation to participate. Since the recruitment of non-donor / non-patient siblings did not result in sufficient numbers for comparative analysis (n=10), these results were not further analyzed.

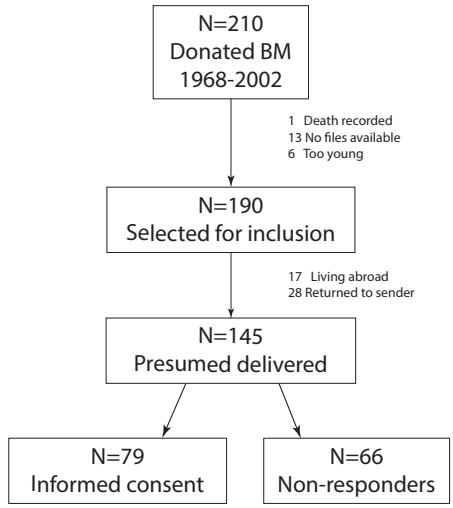

Figure 2: Inclusion and response; excluded donors: 17 donors were living abroad; 6 donors had not reached the age of 12 years at time of the study. One donor had died; 28 donors were untraceable. Thirteen files were no longer available.

At time of the study in total 85 of all recipients had died (35%). All surviving recipients (n=79), who were at least 12 years old, were invited to participate in the study. The total number of FU years was 1340.

Informed consent was received from 79 donors, including four of the donors with a medical condition at the time of donation. At time of the study 91% (71/79) of the donors considered themselves overall healthy. However, 25% (20/79) had developed medical complaints since the BM donation. One donor (donor 071) with congenital heart abnormalities mentioned stent placement at age of 16 years; donor 012 reported the prophylactic use of antibiotics due to his congenital asplenia and heart abnormality. Seven donors mentioned regular upper airway infections, and seven donors reported problems related to asthma of allergies. Furthermore three donors reported having developed autoimmune diseases (rheumatoid arthritis, hypothyroidism and Crohn's disease) since donation. Many other donors reported

non-autoimmune joint problems such as bone fractures and contusions or hospital admissions due to (minor) surgery. Two donors suffered from epilepsy and two others were anemic; none of these donors had a medical history at time of donation. Two donors required medical intervention for severe psychological problems, five suffered from long lasting fatigue. One donor reported persisting back pain since the second time she donated to her sibling. Six donors reported more than one health issue. The majority of the donors had a healthy body mass index both at time of donation and FU, although 33% of the donors were underweight at time of donation, compared to 13% of healthy Dutch children.

Health related Quality of Life (HRQOL): PedsQL, GHQ-12 and SF-36

PedsQL™ 4.0

Donors 12-18 year (n=18) were asked to complete the PedsQL. No significant differences were found between mean scores of child donors and the norm group of healthy school children. However, when taking into account the survival of the recipient, donors with a living recipient (n=13) scored significantly better on the "physical health" domain, than did donors of whom the recipient was deceased (n=5, T-test, p= 0.025). In contrast no significant correlation could be found between the sum scores of the donors and those of their recipients (n=16), suggesting that the health status of the recipient does not influence HRQoL of the donor.

General Health Questionnaire, GHQ-12

The mean total score of the adult donor group did not differ significantly from the healthy adult Dutch population. Socio-demographic and donation-related characteristics, such as marital status, education, gender and recipient survival was not associated with the mean total score or the percentage of psychopathology in the donor group.

Medical Outcome Study Short Form 36, SF-36

All donors had significantly higher (=better) raw scores in the sub domains "physical functioning" (p=0.000), "role physical" (p=0.000), "bodily pain" (p=0.000), "general health" (p=0.000), "social functioning" (p=0.000) and "mental health" (p=0.0034) compared to the general healthy Dutch adult norm group. The difference on the "role emotional" scale was close to significance (p=0.054). Since all of the sub domains, included in the "physical component summary score", differed significantly from the norm group, it was not surprising for this score to be significantly different as well (p=0.000). When comparing male to female donors, male donors scored significantly

better on the sub domains "vitality" (p=0.018) and "mental health" (p=0.030). They also scored significantly better on the "mental health summary score" (p=0.013).

Donors with a living recipient scored significantly better on the "role emotional" sub domain, compared to those with a deceased recipient (p=0.032). No mean differences were found according to education or marital status. There was a significant positive relationship between the "vitality" of the donor and the "vitality" of their recipient (p=0.030). A significant positive correlation was also found between "bodily pain" of the recipient and "mental health" of the donor (p=0.038), "general health" of the recipient and "mental health" of the donor (p=0.028) and "mental health" of the recipient and "bodily pain" of the donor (p=0.037). All of the other sub domains did not show any significant correlations (see Figure 3).

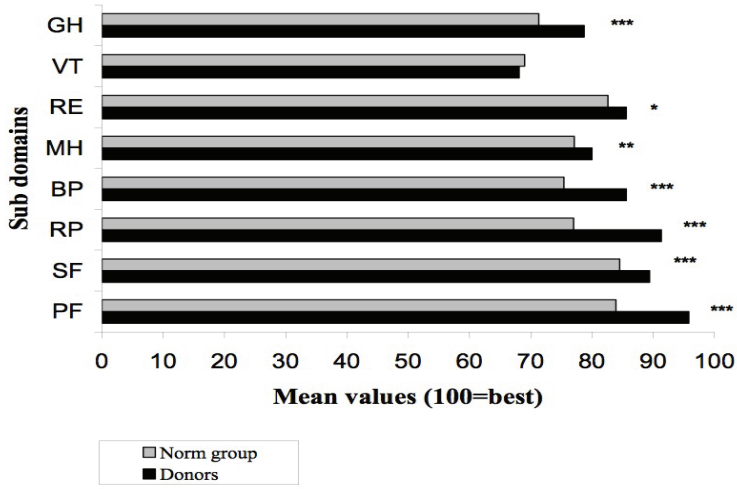

Figure 3: Figure 3: SF-36 subscale means of donors compared to the norm group
GH = general health; VT = vitality; RE = role emotional; MH = mental health;
BP = bodily pain; RP = role physical; SF = social functioning; PF = physical functioning.
*** significance at the <0.001 level; ** significance at the <0.05 level; * not significance

Discussion

This is the first study addressing the immediate effects and long-term somatic and HRQoL outcome of BM donation in a large pediatric cohort. The Leiden unit performed the first European pediatric sibling BM transplant over four decades ago. As such the unit has considerable expertise and experience in the management not only of pediatric patients, but also of child donors. We anticipated that our results may be influenced depending upon the year of donation, since the study spanned a considerable period of time. Over this period clinical practice and ethical

considerations have changed. We were able to retrieve a substantial amount of information from archived medical files and the hospital computerized information system, which similarly was not compromised by year of donation, allowing us to confidently report our long term follow-up findings. This is particularly important, as to date no other published data is available for such a comprehensive study on pediatric donors. Recently the Pediatric Diseases Working Party of the EBMT, reported the early side effects of childhood stem cell donation[35], in a prospective study. This study differs from our report as all age groups were included and both bone marrow and peripheral blood stem cell donation and FU was only 1 year post donation. However, their observations confirm our findings that large volume harvests are associated with significant reduction in hemoglobin levels and the need for allogeneic transfusion. Also children ages less than 4 years were more likely to experience events. Furthermore, in the US the RDSafe Study, which is ongoing, is collecting extensive clinical and psychosocial information from a sample of 100 pediatric stem cell donors.

Donor Eligibility

During the study period the major accepted criteria for donor eligibility were being a sibling and an HLA match. The lack of well defined criteria for pediatric donors may well explain the fact that donors were declared fit to donate despite a concurrent medical condition. Although partly explained by the early years of transplantation included in our study, our analysis and recent publications show that the care for related donors is still, even in large transplant centers, in development[12,13], compared to unrelated donors. Our study shows there is a wide variance in the management of pediatric donors, suggesting that donor eligibility criteria specifically designed for children would be helpful for pediatric transplant physicians. Potential donors with co-morbidity might place an additional burden on parental consent, which may disadvantage the welfare of the donor[1].

Laboratory results and donation procedure

The retrospective nature of our study did not permit us to investigate if donors were or were not routinely evaluated. This in part may be explained by the fact that laboratory results predating computer datasets (i.e. before 1995) were less available. Interestingly the unit policy of routine morphological BM examination of sibling donors at the time of harvest, allowed for a comprehensive review of BM, especially in relation to iron stores, irrespective of year of donation. Literature on the composition of healthy infant BM is scarce and concerns cellularity and classification of normal cells, without special attention for iron stores[36,37]. The fact that two-thirds of the reviewed BM smears showed reduced or absent iron stores, suggests that FU regarding hematological recovery, pertinent to iron status and where applicable oral

iron suppletion in young pediatric donors is necessary. This should include serological assessment of iron stores. In our study, the relationship between BM iron stores and serological parameters could not be assessed, as the latter was not routinely undertaken. It is not clear whether autologous red cell collection affected iron stores. The importance of maintaining normal iron stores is relevant in the pediatric age group, as iron deficiency has been associated with delayed neuro-cognitive development and poor school function[38], especially in early school age.

Harvesting procedure

In this study harvest volumes often exceeded 20 ml/kg (which is the standard in (un)related adult donation, equivalent to approximately 20% of total circulating volume)[19,39,40]. Although only approximately 10% could be explained by major ABO incompatibility and/or poor cell yield, we were unable to determine the reason for large volume harvests, especially in the donors donating to younger siblings included in this study. The large volumes harvested frequently resulted in a, unnecessary high cell dose for the related setting. Since 2007 our department has limited the harvest volumes to 15ml/kg donor body weight. An analysis of 43 donations undertaken since implementation showed full engraftment in 41 recipients (100% donor), stable mixed chimerism in 1 child with homozygous ß-thalassemia (transfusion independent) and 1 late rejection in a child transplanted for homozygous ß-thalassemia. Our data suggest that limiting the harvest volume does not impede successful cell yields sufficient for engraftment for the vast majority of children. Recent analysis (data not provided) in our department, shows that in the past 5 years, we have limited our collection volumes for child donor to this standard, without compromising the graft. Erythrocytes from the graft were re-infused in all donors to reduce post harvest anemia. Pertinently, in more than half of all donors in our study, when harvest volumes exceeded 15 ml/kg, allogeneic blood transfusion was necessary to compensate for the blood loss, with the additional risks involved[41,42].

Long-term FU & Health Related Quality of Life (HRQoL)

Although this study is based upon a self-reported questionnaire, this is the first attempt at documenting the donor's perception of HRQoL following childhood donation. Since there is no comparable data available, the response rate was compared published data from prospective studies (involving both related and unrelated donors). An overall response of 38% of all donors in the study period responded to the questionnaire, however, considering that only 145 invitations were presumed delivered, this figure rose to 54%. Participation in our study was equally distributed throughout the study period. In comparison, Hoelig *et al.*[43] reported a five year post donation FU response of only 42% in unrelated donors. The experience in Austria with related donors was even lower, with a response of less than 10%, ten

years post donation (personal communication A. Rosenmayr). As in all retrospective studies of a self reporting nature, the results could be influenced by the non-response bias[44]. The recollection of the donation and the period following may have been influenced by the lapse of time or the recipient's death. More than half of donors with medical problems at time of the donation responded to the questionnaire (4 out 7, see Table 2). Although continuing medical problems were reported, none were directly related to the donation procedure. The reporting of non-specific clinical problems, such as recurrent upper airway infections and joint problems are difficult to interpret, and most likely do not reflect a long term consequence of BM donation in early childhood. However, as the participants felt them sufficiently relevant to report, we included them for completion. The study was not designed to verify self reported medical conditions. With this study an attempt has been made to disclose aspects of pediatric donor care.,

On average 16 years post donation, adolescents and adults function remarkably well, both physically and mentally. Higher raw scores on the SF-36 as observed in our study have also been reported in living kidney donors[45-48]. It is unlikely that this phenomenon is directly related to the donation procedure. However, it has to be mentioned that the age range of the comparative SF-36 Dutch adult norm group (mean 43.1 yr) is higher than those of the adult donors (mean 23.9 yr) in our study, which may explain the observed differences. Male donors scoring better than female donors on "vitality" and "mental health" sub domains of the SF-36 questionnaire, is consistent with the findings of published data[30,49]. Our findings that donors whose recipient was alive, compared to donors who were bereaved, scored significantly better on the "role emotional" sub domain. This is similar to findings among living kidney donors[50], but contrary to findings of bereaved related donors in the USA[16]. One explanation of our findings may be that the impact of bereavement at a young age may cause difficulties in adaptation and emotional development in adulthood[7].

In children, donors of living recipients scored better on the "physical health" domain than did donors of a deceased recipient. The occurrence of physical problems in children has been shown to predict internalizing problems such as depression and anxiety and externalizing problems, such as aggressive or acting-out behavior at a later age[51]. Our study suggests that these problems may persist into adulthood in selected cases of child donors. Encouragingly only two donors reported severe psychological difficulties.

Although the donation procedure involves no physical therapeutic benefit for the donor, the psychological benefit of being able to help a sick family member is evident[9,16]. This might justify a limited amount of risk for a healthy child who is due to age limitations not able to give informed consent[1,25,52].

We were unable to address the issue of informed consent at the time of donation as the study was limited by its retrospective nature. However, consent in the pediatric population remains an important issue to be addressed in future studies. To what extent pediatric BM donation is still a voluntary act, is questionable. MacLeod *et al.*[9] reported that two-thirds of sibling donors had 'deliberate no choice', while the remainder felt 'forced' or coerced to participate. Contrary to the adult (un)related donor practice, informed consent is rarely requested from young children. Young children have a right to be informed[4,53] before committing them to undergo invasive procedures, especially when the intervention is not to their direct medical benefit. Careful consideration should be given at all times to weigh the balance of risks and benefits to the donor[54].

Conclusions and recommendations

BM donation in early childhood does not lead to significant physical or psychosocial impairment at a later stage in the majority of donors. However, the lack of accepted guidelines for child donor care management leads to inconsistencies in the procedures, even in a single centre. Our study highlights the importance of independent medical assessment of child donors, especially in children with pre existing medical conditions to avoid peri-donation events. The limitation of the maximum harvested volume to 15 ml/kg donor body weight prevents young children being exposed to allogeneic blood products. Our study would suggest this would not be detrimental in terms of poor cell yields, to the recipients.

Low iron stores were frequently detected in our study population, suggesting that hematological follow-up pertinent to iron status is desirable and where necessary oral iron suppletion should be prescribed.

Although this study has shown that BM donation in early childhood does not negatively affect a donor's life on long-term, it is important to weigh the risks and benefits and thus safeguard the interests of the child donor.

Conflict of interest statement

The authors declare there are no conflicts of interest.

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