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# Total-Body Irradiation is a major risk factor for young adult onset diabetes mellitus and hyperlipidemia in childhood cancer survivors after hematopoietic stem cell transplantation.

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## Background

- Type 2 DM(T2DM) and hyperlipidemia(HL) are one of the late adverse effects of HSCT(1)
- Total body irradiation (TBI) have been reported to possibly cause T2DM and HL.
- Clinical details of T2DM and HL after HSCT are not clarified yet.

## Aim

- Identifying risk factors for T2DM and HL after HSCT
- Clarifying clinical details of T2DM and HL after HSCT

## Patients

Alive patients underwent HSCT at TMDU from 1983 to 2012 (91)

Malignancy (43) | Non-malignancy (42)

**Followed up continuously as CCSs (24) →Analysed retrospectively**

Not followed up(19)

## Methods

Clinical profiles of 24 patients

- Type of malignancy: Acute lymphoblastic leukemia(ALL) [n=13] /other malignancy [n=9]
- Conditioning regimen: With TBI [n=10] or without TBI [n=10]
- Obesity: BMI SDS (standard deviation score)
- Prevention therapy for cGVHD: tacrolimus administration (+[n=8] or –[n=9])

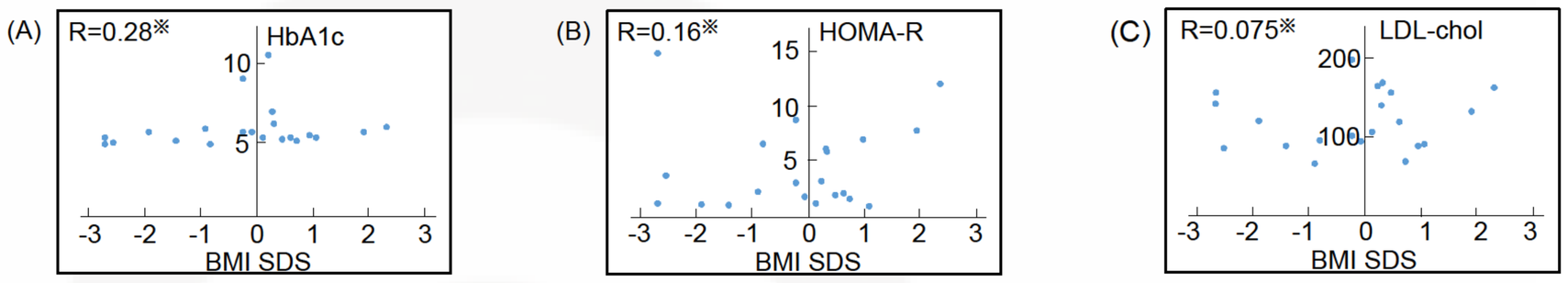
## Six out of twenty four eligible patients(25%) developed T2DM or HL (Table 1)

| Pt.(Sex) | Disease | TBI | BMI SDS[a] | tacrolimus | Age at HSCT | Age at Onset of T2DM/HL | Yrs from HSCT | T2DM | HbA1c[a] (<6.5%) | HOMA-R[a] (<2.5) | HOMA-β[a] (>40) | U-CPR[a] (>29.7μg/day) | HL | LDL-chol[a] (<140mg/dl) | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 (F) | ALL | + | 0.30 | + | 1 | 11 | 10 | + | 6.9 | 6.0 | 289 | 204 | + | 139 | BG+Statin |
| 2 (M) | ALL | + | 0.23 | N.A | 5 | 15 | 10 | + | 10.2 | 2.9 | 21 | 59.9 | + | 165 | BG+insulin+Statin |
| 3 (F) | ALL | + | -0.18 | N.A | 2 | 18 | 15 | + | 8.8 | 8.8 | 100 | 31.9 | + | 200 | BG+Statin |
| 4 (F) | ALL | + | 0.32 | - | 2 | 15 | 13 | + | 6.2 | 5.7 | 264 | 105 | + | 169 | BG+Statin |
| 5 (M) | ALL | + | N.A | N.A | 18 | 25 | 7 | - | 5.7 | 1.6 | 108 | N.A | + | 215 | Statin |
| 6 (F) | Sarcoma | - | -2.43 | - | 14 | 19 | 5 | - | 5.0 | 15.3 | 373 | N.A | + | 156 | Statin |

a) Data at diagnosis of DM or HL
BG: biguanide

1) All patients who developed T2DM had HL
2) All (4/4) T2DM patients and 5/6 HL patients underwent TBI
3) No obesity in T2DM or HL patients (BMI SDs of all patients were < +1.0.)
4) Insulin resistance would be the major cause for T2DM from the data of HOMA-R, HOMA-β, and U-CPR.

## BMI SDS did not associate with values of HbA1c/HOMA-R/LDL (Fig. 1 A~C)




1) Higher BMI was not the risk for T2DM/HL after HSCT.

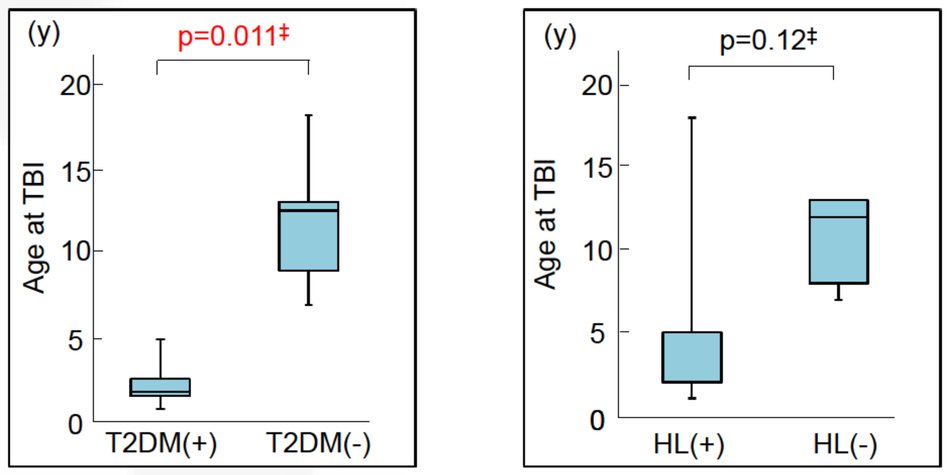
※) Spearman's rank correlation coefficient
All the coefficients showed no significancy.

## Only TBI was associated with T2DM/HL (Table 2)

| | T2DM(+) | T2DM(-) | p | HL(+) | HL(-) | P |
|---|---|---|---|---|---|---|
| ALL | 3 | 10 | 0.45† | 4 | 9 | 0.52† |
| Not ALL | 1 | 8 | | 2 | 7 | |
| TBI(+) | 4 | 6 | 0.043† | 5 | 5 | 0.016† |
| TBI(-) | 0 | 10 | | 0 | 10 | |
| BMI SDS | 0.27 [0.13-0.3] | -0.04 [-1.3-0.7] | 0.79‡ | 0.027 [-0.74-0.26] | -0.052 [-0.92-0.75] | 0.79‡ |
| FK506(+) | 1 | 7 | 0.74† | 1 | 7 | 0.55† |
| FK506(-) | 1 | 8 | | 2 | 7 | |

†) Fisher's exact test ‡) Mann-Whitney U test

## Younger age at TBI was the risk for T2DM (Fig. 2)




1) Multivariate analyses confirmed that TBI was an independent risk for T2DM.

‡) Mann-Whitney U test

## Discussion

- TBI is the risk for T2DM and HL without obesity.
- Prevalence of T2DM in TBI patients was 40% in our study, consistent to that of previous studies, from 20%(2) to 60%(1).
- This is the first study to show TBI at younger age is a risk for T2DM.

A previous study(1) reported the age at TBI was not a risk for DM.

One of the possible reason for the discrepancy is that the patients in our study received HSCT at younger age than the previous study.

We speculate that TBI at younger age, especially less than 5 yrs increase the risk for DM.

- The risks of TBI should be considered for selecting conditioning regimen of HSCT, especially, for young children.

## Conclusion

**Regarding the late adverse effects of HSCT, TBI, especially at younger age, is one of the major risks for T2DM and HL**

## References

1. Taskinen et al. Lancet. 2000;356:993-997
2. Shalitin et al. Bone Marrow Transplant. 2006;37(12):1109-1117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