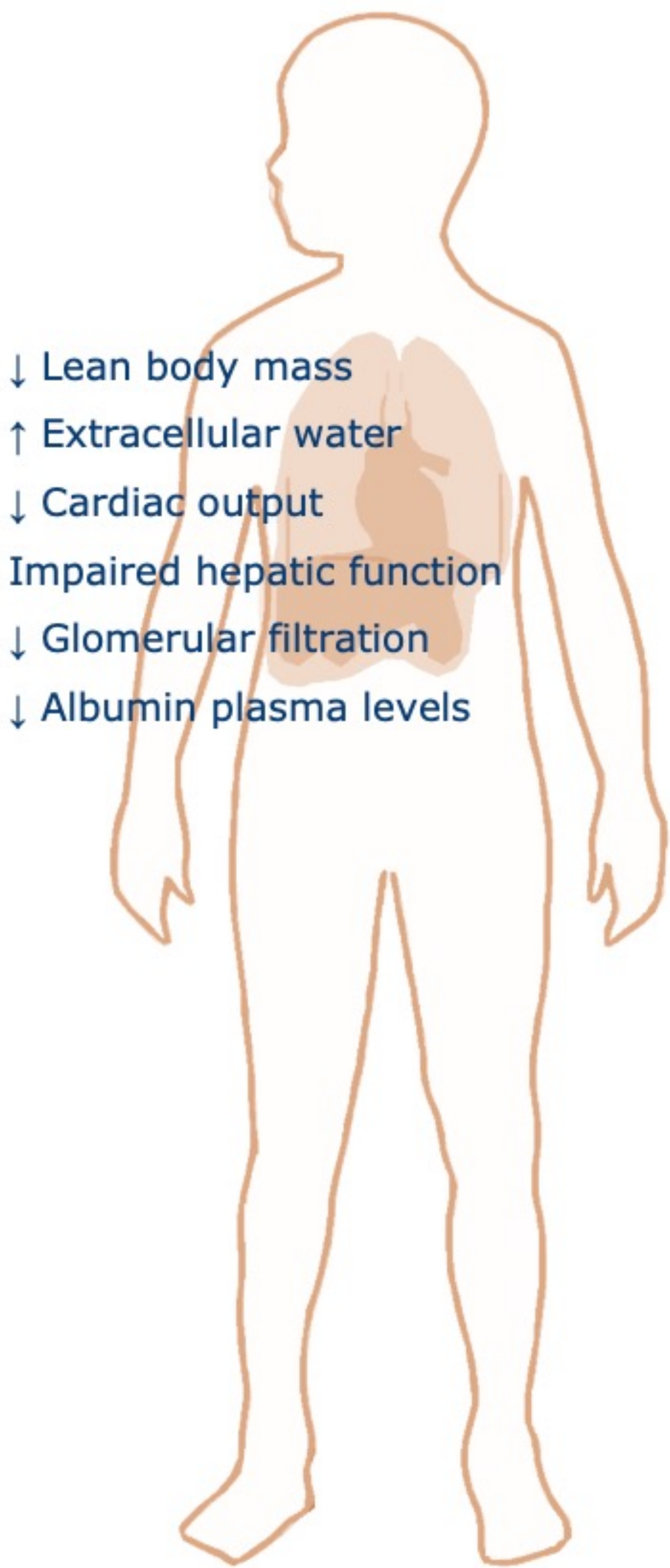


Impact of Undernutrition on Pharmacokinetics of Chemotherapy in Children with Cancer: A Systematic Review

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Background

- Undernutrition is one of the largest global health problems in children: it is related to almost half of the deaths in children under the age of 5.
- **Undernutrition affects up to 60% of the newly diagnosed children with cancer in LMICs and may be exacerbated by delays in cancer diagnosis and treatment.**
- Undernutrition causes metabolic changes and thereby may affect tolerance and/or efficacy of chemotherapy by altering pharmacokinetics of the drugs.
- Data on animals and adults describe pharmacokinetic alterations
- **Optimal drug dosing in undernourished children is crucial to optimize outcomes on these vulnerable patients.**

Aim

To provide **an overview of the effect of undernutrition on the pharmacokinetics of chemotherapy in children with cancer** to serve as a foundation for future research and insight into optimal chemotherapy dosing in this population.

Methods

- This systematic review is performed according to the PRISMA guidelines. PubMed, EMBASE and Cochrane databases were searched in October 2021 using the following key search terms: ‘pharmacokinetics’, ‘antineoplastic agents’, ‘malnutrition’, and ‘child’.
- Independently abstract en full-text screening.
- Risk of bias: Quality Assessment Tool for Quantitative Studies by EPHPP.
- Main outcomes: **pharmacokinetic parameters in undernourished and non-undernourished children.**
- Nutritional status was defined following WHO’s definition, WHO’s growth reference data and Gomez’ classification.

Results

- Four studies were included, with a total of **123 (18%) undernourished patients.**
- Patients received different types of chemotherapies: methotrexate, vincristine, doxorubicin, etoposide, teniposide, cytarabine or mercaptopurine.

Study	Pharmacokinetic parameters	Malnutrition	Normal nutritional status	P-value
Methotrexate				
Hijiya <i>et al.</i> (2006)	Mean CI (±SD) (in mL/min/m²)	111.1	114.1	0.47 ^a
Kumar <i>et al.</i> (1987)	Mean CI (±SD) (in mL/min/m²)	1.0 (0.7)	1.0 ^c	0.43
	V_d (±SD) (in L)^b	18.2 (13.0)	20.9 ^c	0.43
Vincristine				
Israels <i>et al.</i> (2010)	Mean CI (±SD) (in mL/min/m²)	244.9 (76.0)	519.0 (200.9)	<0.05
	Mean AUC (±SD) (in µg/mL min)	6.3 (2.3)	3.4 (2.1)	0.01
Doxorubicin				
Thompson <i>et al.</i> (2009)	Mean CI (±SD) (in mL/min/m²)	401.7 (8.5)	436.7 (4.5)	NS ^a
	V_d (±SD) (in L/m²)^b	7.0 (3.4)	7.3 (2.0)	NS ^a
Etoposide				
Hijiya <i>et al.</i> (2006)	Total XIIB Mean CI (±SD) (in mL/min/m²)	43.6	48.7	0.41 ^a
Cytarabine				
Hijiya <i>et al.</i> (2006)	Total XII Mean CI (±SD) (in mL/min/m²)	852.2	773.8	0.56 ^a
Teniposide				
Hijiya <i>et al.</i> (2006)	Total XII Mean CI (±SD) (in mL/min/m²)	14.2	14.0	0.35 ^a

NA = no data available; BMI = body mass index; CI = clearance; AUC = area under curve; V_d= volume of distribution; SD = standard deviation; NS = not significant.
^aP-values obtained between four groups. At risk for overweight and obesity groups are not shown in Table 2.
^bV_d is noted in the initial phase, thus its behavior in the central component.
^cBased on one patient.

Discussion

- **Pharmacokinetic parameters vary among children with normal nutritional status and undernourished children but was only statistically significant for vincristine.**
- Significant associations are described between undernutrition and toxicity (severe neutropenia, severe infection, sepsis).
- Pharmacogenetics must be considered too since small variations between populations might affect pharmacokinetics of chemotherapy.
- The degree of undernutrition may not be representative of the true pharmacokinetic effect of undernutrition, particularly in LMICs, and may underestimate the impact on drug disposition.

Conclusions

- **Evaluating chemotherapy pharmacokinetics in undernourished children is crucial to administer effective and safe treatment and contributes to the WHO’s aim to achieve over 60% survival in 2030 for children with cancer worldwide.**
- **Pharmacokinetic studies among severely undernourished children in LMICs are highly needed to investigate this important topic.**

