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Review article

# A review of GI conditions critical to oral drug absorption in malnourished children

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ABSTRACT

Accurate prediction of oral absorption of drugs relies on biorelevant methodology. Current methods are based on Western healthy adult populations. Malnourished children have many differences in their gastrointestinal anatomy and physiology compared to a healthy Western adult. These differences may affect the oral absorption of medicines and it is important to gather knowledge on these GI differences in order to develop biorelevant predictive methods for this vulnerable population.

A literature search was conducted within PubMed and Scopus to identify papers that describe how gastrointestinal physiology and anatomy is altered in malnourished children. Relevant data was extracted and a narrative review generated to describe how GI differences may affect oral drug absorption.

Several differences in GI anatomy and physiology were reported in the literature including: reduced saliva secretion; increased gastric pH; slower gastric emptying; increased levels of bacteria in the small intestine; reduced surface area of intestinal villi and increased intestinal permeability. Much of the data was more than 30 years old and referred to a heterogeneous malnourished population.

Sufficient data has been identified that will inform basic novel biorelevant methods to predict oral drug absorption in malnourished children. Further work is required to generate additional data to improve these models and also to verify the models with appropriate pharmacokinetic data.

## 1. Introduction

When administering an oral drug product to a patient there are various factors which are important to ensure sufficient drug absorption; these include drug- and formulation-related parameters like drug solubility and permeability, drug product dissolution and gastrointestinal (GI) conditions including the composition and physicochemical properties of GI fluids, transit time and gut wall conditions relevant to metabolism, passive diffusion and active transport of drugs. GI physiology is therefore a key aspect that determines the *in vivo* performance of orally administered drugs.

Over the last decades, bio-predictive *in vitro* models have been established for predicting oral drug exposure for a number of compounds in adults after dosing either in fasted or fed conditions. There is a lack of such *in vitro* models for children, yet they are urgently required to better predict the *in vivo* performance of medicines in children to minimize the burden of clinical testing. When developing biorelevant *in vitro* media and models to simulate gastrointestinal conditions, the most appropriate environment needs to be represented. It is already known that there are differences in the gastrointestinal physiology of children in different age groups and in comparison to adults, which are accompanied by variable volumes, pH values and composition [1]; it is obvious that these differences will be different again in children suffering from diseases affecting GI conditions or in malnourished children.

Malnutrition is a condition that is reported for several patients groups and can be quite common in hospitalized and elderly patients [2–4], pregnant and breastfeeding women, and children [5]. Due to their high nutritional requirements children are more susceptible to malnutrition than adults [6]. When designing appropriate bio-predictive *in vitro* models, it will be essential to consider the specific GI features of malnourished children. To date, a review of the GI conditions in malnourished children is not available. However, it is obvious, that malnutrition will alter the GI environment. An altered GI environment may affect pharmacokinetics of orally administered drugs, which in turn may affect efficacy and subsequent therapy. In basic

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**Table 1**
Most common used classification criteria of the nutritional status of children since 1956.

| Classification criteria | Definition | Type of classification | Advantages | Disadvantages |
|---|---|---|---|---|
| Gomez et al. (1956) [20] | Body weight ranges as a percent of the theoretical average in relation to the age:<br>- protein energy malnutrition (PEM) I: 76–90%<br>- protein energy malnutrition (PEM) II: 61–75%<br>- protein energy malnutrition (PEM) III: ≤ 60% | Quantitative classification into mild, moderate and severe cases<br>Indication for acute malnutrition (wasting) | | The percent-of-average method does not take into consideration the variability of the average<br>In many communities the ages of children are not known<br>Application of the Gomez index requires the use of an external standard for comparison & different external standards are used in different studies |
| McLaren et al. (1967) [21] | Scoring system (for details see the reference) for protein calorie malnutrition that includes: oedema; dermatosis; hair change and hepatomegaly in combination with measured serum albumin<br>- 0–3: marasmus<br>- 4–8: marasmic-kwashiorkor<br>- 9–15: kwashiorkor | Qualitative classification to distinguish marasmus, kwashiorkor and marasmic kwashiorkor | | |
| Wellcome classification, 1970 | Combines weight and the presence/absence of oedema to classify terminology<br>**Weight* (% of standard)** / **Oedema: Present** / **Oedema: Absent**<br>80 - 60 / Kwashiorkor / Undernourished<br>< 60 / Marasmic kwashiorkor / Marasmus<br>* standard = 50th percentile Boston values | Qualitative classification to distinguish marasmus, kwashiorkor and intermediate forms | | |
| Waterlow et al. (1976) [22] | According to Johansson et al. 1994 [23]: height-for-age<br>- normal: > 95%<br>- mild/PEM I: 90–95%<br>- moderate/PEM II: 85 - < 90%<br>- severe/PEM III: < 85% | Quantitative classification into mild, moderate and severe cases<br>Indication for chronic PEM (stunting) | | |
| National Center for Health Statistics (NCHS), 1978 | Categorization of the nutritional status of children with the aid of standards for<br>- weight-for-age<br>- length-for-age<br>- weight-for-length<br>- head circumference-for-age<br>and Z (standard deviation)-scores: $Z-\text{score} = \frac{(\text{actual anthropometric value} - \text{median reference value})}{\text{standard deviation}}$<br>- indicates a nutritional status equal to the median for a child of the same gender<br>- ≤0.00 indicates a nutritional status that is the indicated number of standard deviations below the median for a child of the same gender and age:<br>- For example children of 0–5 years<br>- severe malnutrition: any z-scores ≤ −2<br>- questionable malnutrition: any z-scores > −2 and ≤ −1<br>- normal weight: all z-scores > −1<br>- ≥0.00 indicates a weight-for-age that is above the median for a child | Quantitative classification into mild, moderate and severe categories | Z scores reflect the reference distribution and are comparable across ages and indicators [24] | Percent-of-median method does not take into consideration the variability in the relative width of the distributions of the different indicators [24]<br>The data used to construct the reference came from a longitudinal study of children (0–3 years) from a single community in the United States. The children have rarely been measured (every 3 months), which is inadequate to describe the rapid and changing rate of growth in early infancy [25] |

(*continued on next page*)

**Table 1** (*continued*)

| Classification criteria | Definition | Type of classification | Advantages | Disadvantages |
|---|---|---|---|---|
| WHO Child Growth Standards, 2006 [25] | Categorization of the nutritional status of children with the aid of standards and Z-scores for:<br>- length-for-age<br>- height-for-age<br>- weight-for-height<br>- weight-for-age Z-score (WAZ)<br>- weight-for-length Z-score (WLZ)<br>- weight-for-height Z-score (WHZ) | Quantitative classification into mild, moderate and severe cases | In contrast to NCHS standards these standards include children from around the world: Brazil, Ghana, India, Norway, Oman, USA [25]<br>Z scores reflect the reference distribution and are comparable across ages and indicators [24] | |
| Body Mass Index (BMI) | Weight in kg divided by square of height in cm:<br>- BMI percentile for age < 5: underweight<br>- BMI percentile for age ≥ 5 or < 85: healthy weight<br>- BMI percentile for age ≥ 85 or < 95: overweight<br>- BMI percentile > 95: obese | | | |

terms the absorbable dose is influenced by the transit time; concentration of drug at the absorbing surface; surface area available for absorption and the permeability of the drug across the membrane. Differences in any of these parameters will affect the fraction of dose absorbed; hence predictions made in a healthy population may be very different to those where the GI parameters are different. A detailed understanding of the nature of specific GI parameters in malnourished children and of how much they may affect timing, site and extent of *in vivo* drug release seems to be one of the key factors for developing better oral medications for these children. Moreover, any *in vitro* and/or *in silico* models that consider these relevant GI parameters and would be applicable to predict the *in vivo* performance of orally administered drugs in malnourished children would be extremely beneficial with regard to increasing the safety and efficacy of oral medicines provided to this patient group.

The group of malnourished patients describes a heterogenous population. Malnutrition refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients. Malnutrition is divided into undernutrition, which includes stunting, wasting and underweight, and to overweight, which includes obesity and several diet relevant diseases as heart disease and cancer [7]. Undernutrition is caused by a lack of food in general, but also by inadequate, unhealthy diets and diseases including digestive and absorptive disorders resulting in micronutrient deficiencies. It makes children in particular much more vulnerable to disease and death and is responsible for approximately 50% of child mortality for those under five years old [8]. According to the latest United Nations International Children's Emergency Fund (UNICEF)/World Health Organisation (WHO)/World Bank Group Joint Child Malnutrition Estimates (May 2018) at least 202 million children worldwide are stunted or wasted [8].

In the literature, different criteria that have been applied to classify the nutritional status of children can be found (Table 1). According to current WHO criteria undernutrition can be present in 4 broad subforms, i.e. underweight (low weight-for-age), stunting (low height-for-age), wasting (low weight-for-height) and deficiencies in vitamins and minerals [7].

The main hallmark of child malnutrition is growth retardation. Underweight, which represents low weight for age [7], is defined as a weight-for-age at least two standard deviations below the median weight based on the WHO child growth standards [9,10]. "Stunting" is a term for chronic undernutrition and reflects low height for age [7]; defined as less than two standard deviations (SD) below the WHO standards [9,10]. Acute undernutrition is termed "wasting", where moderate wasting is indicated by a weight between two and three SDs below the WHO standards [9,10]. Severely wasted children have a weight of less than three SDs below the WHO standards or a mid-upper arm circumference (MUAC) of less than 115 mm in children of 6–60 months [9–11].

"Severe wasting" and bilateral oedema are independent diagnostic criteria for severe acute malnutrition (SAM), which is associated with a high risk of death and which requires urgent therapeutic feeding [11].

Protein-calorie malnutrition (PCM) is a specific subtype of SAM with a deficiency in macronutrients including protein, carbohydrates and fat. The WHO defines PCM, also known as protein energy malnutrition (PEM), as "a pathological condition that results from a lower ingestion of protein and calories, which occurs more frequently in children under five years of age". Severe PCM can be categorized into three principal clinical forms: (i) marasmus, an acute malnutrition characterized by severe wasting of fat and muscle and a gross underweight status; (ii) kwashiorkor presents with moderate growth retardation and bilateral pitting oedema; and (iii) marasmic kwashiorkor, the most severe form of PCM, a mixed form of both marasmus and kwashiorkor that is characterized by the presence of both wasting and bilateral pitting oedema [12].

PCM is a major public health problem affecting a high proportion of infants and older children worldwide and accounts for a high childhood

morbidity and mortality in the developing countries. Its association with a wide spectrum of infections necessitates multiple drug therapies. Whereas the epidemiology of PCM has been extensively studied globally, the pathophysiological changes that may affect disposition of these drugs in malnourished children have not been reviewed in that much detail [13]. Oshikoya et al. [14] performed a systematic literature review to determine the effects of PCM on drug pharmacokinetics and concluded that there have been relatively few pharmacokinetic studies of drugs frequently used for treatment of children with PCM. However, they also present case examples in which decreased absorption of drugs such as carbamazepine [15], chloroquine [16], sulphadiazine [17], and chloramphenicol [18] have been reported in children with PCM when compared with healthy normal children and was attributed to morphological changes in the jejunum. In addition, treatment failure with artemether-lumefantrine was reported to be due to incomplete absorption in a malnourished child [19].

The aim of this review was to review the available data on the gastrointestinal anatomy and physiology of malnourished children relevant to the performance of orally administered medicines. The focus was set on the screening of the particular features of undernutrition. Thus, in the following sections, the terms malnutrition and undernutrition can be regarded as interchangeable.

## 2. Materials and methods

A literature search was conducted within PubMed and Scopus using the search terms listed in Fig. 1.

Literature that provided original data on parameters that affect GI physiology associated with oral administration and absorption of drugs were included in further analysis. Specifically literature that reported aspects on gastrointestinal transport, motility or contents was sought. Studies where children had co-morbidities were also included in the analysis.

The search was conducted between September 2017 and March 2018. The search results were sorted by the authors (LF and EP-S) based on titles, abstracts or full text articles. Additional literature was obtained from reference lists of the identified articles or reviews on this topic.

For data extraction, studies were sorted according to whether they investigated oral cavity, gastric, small intestinal or large intestinal parameters. Further sorting permitted papers to be reviewed based on physiological parameters of these regions. Data was extracted from relevant papers to gather evidence that was summarized for each absorption parameter. There was too much heterogeneity in the identified literature which did not permit a systematic meta-analysis. Therefore the results could not be presented as a systematic review. Thus, a narrative review was selected to discuss reported effects of malnutrition that would impact on oral drug absorption considering the process from the initiation of oral ingestion to excretion.

## 3. Results

*Definition of malnutrition used in the papers identified.*

The wide range of criteria used to classify malnutrition was highlighted in Table 1 and the papers identified used a range of these criteria when reporting results. The NCHS criteria were the most commonly used with the Gomez index, the Wellcome classification and WHO child growth standards being used in multiple studies [23,26–43].

### 3.1. Oral cavity

The oral cavity is the site of administration for oral medicines. Solid oral dosage forms are usually designed to be swallowed whole and to release the drug in the stomach and/or intestine. However, in children solid oral dosage forms might not be swallowed as rapidly as in adults. Thus, there is a chance that conditions in the oral cavity such as pH, buffer capacity and composition of saliva affect both integrity and drug release from solid oral dosage forms and consequently affect *in vivo* drug release. Dosage form integrity could be affected by mechanical forces caused by tongue and palate as well as by the volume, pH, buffer capacity and composition of saliva. Salivary pH and buffer capacity also play an important role in dental diseases and compared to healthy children a higher incidence of caries and other dental diseases have been observed in children with poverty driven malnutrition [44,45].

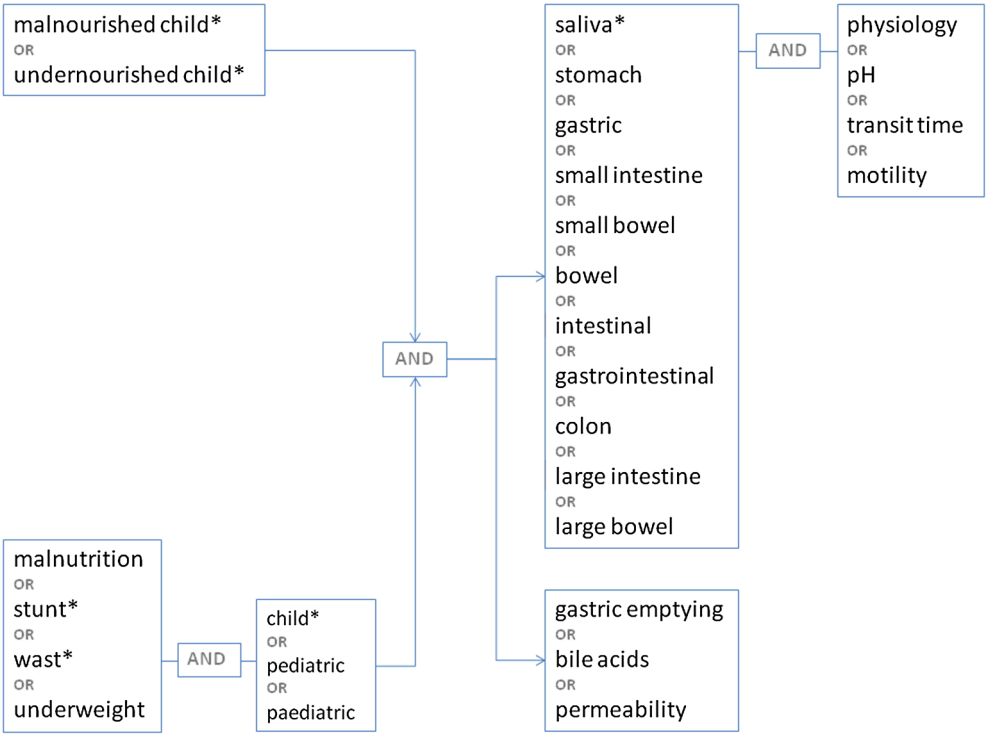


**Fig. 1.** Search terms used in the literature search.

**Table 2**
Saliva parameters.

*(a) Summary of data on changes in salivary secretion*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Agarwal et al., 1984 [30] | 52 patients and 42 healthy controls<br>Age: 1–10 years<br>Study conducted in Varanasi, India | Gomez index (weight-for-age): mild, moderate and severely malnourished | Time of saliva collection | Longer collection time for a defined volume of saliva in severely malnourished children compared to control group | Small study<br>Correlation and regression analysis |
| Johansson et al., 1992 [32] | 34 Indian patients and 34 controls (healthy or mild PEM)<br>Age: 8–12 years | Gomez index (weight-for-age): mild, moderate and severely malnourished | Saliva collection | Reduced stimulated saliva secretion in moderate or severely malnourished children compared to control group | Small study<br>Well described study<br>Statistical analysis |
| Psoter et al., 2008 [35] | 1017 Haitian children<br>Age: 11–19 years | NCHS (weight-for-age): severely and questionable malnourished | Saliva collection | Reduced saliva secretion in malnourished children compared to children without malnutrition | Retrospective cohort design<br>Loss of follow-up not comprehensible<br>Large patient group<br>Methods well described<br>Statistical analysis |

*(b) Summary of data on changes in salivary pH and buffer capacity*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Bud et al., 2017 [45] | 37 Romanian patients and 87 controls (healthy, normal weight or overweight)<br>Age: 6–12 years | Body Mass Index: underweight | CRT buffer strips | Reduced saliva pH in malnourished children compared to control group<br>Reduced saliva buffer capacity in malnourished children compared to control group (not statistically significant) | Small study<br>Statistical analysis |
| Johansson et al., 1992 and 1994 [23,32] | 34 Indian patients and 34 controls (healthy or mild PEM)<br>Age: 8–12 years | Gomez index (weight-for-age): mild, moderate and severely malnourished | Final pH after air was bubbled for 20 min into a mixture of saliva and HCl | Salivary buffer capacity decreased with increasing level (severity) of malnutrition, however, subjects in the control group had a markedly lower buffer capacity which was most probably due to genetic/ethnic effects (African study group vs. Swedish control group) | Small study<br>Well described study<br>Statistical analysis |

*(c) Summary of data on changes in saliva composition*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Agarwal et al., 1984 [30] | 52 patients and 42 healthy controls<br>Age: 1–10 years<br>Study conducted in Varanasi, India | Gomez index (weight-for-age): mild, moderate and severely malnourished | Protein measurement with Folin-phenol reagent<br>Measurement of enzyme arginase activity with centrifuge column technique | Reduced saliva protein and enzyme levels in all malnourished children compared to control group | Small study<br>Correlation and regression analysis |
| Johansson et al., 1994 [23] | 34 Indian patients and 34 controls (healthy or mild PEM)<br>Age: 8–12 years | Gomez index (weight-for-age): mild, moderate and severely malnourished | Coomassie blue method<br>Degradation of insoluble blue-colored starch polymer<br>Anatomic absorption<br>And other | No effect on saliva protein and enzyme levels in moderate or severely malnourished children compared to control group<br>Reduced concentrations of calcium and chloride in moderate or severely malnourished children compared to control group | Small study<br>Well described study<br>Statistical analysis |
| McMurray et al., 1977 [31] | 44 Colombian patients and 27 healthy controls<br>Age: 1.5–2 years | Gomez index (weight-for-age): mild and severely malnourished | IgA concentrations with Immunodiffusion plates<br>Protein measurement with Folin-phenol reagent, aminopeptidase measurement by hydrolysis of L-methionyl β-naphthylamide in Tris-HCl buffer at pH 8.0 | Reduced saliva IgA concentrations in all malnourished children compared to control group<br>No effect on saliva protein and enzyme levels in all malnourished children compared to control group | Small study<br>Statistical analysis<br>Classification system of malnourished children: Gomez index → no standard defined |

Increased residence time and drug release in the oral cavity can increase systemic drug absorption across the oral mucosa. Therefore, mucosal integrity is also an important fact to consider when discussing drug administration to malnourished children.

#### 3.1.1. Salivary secretion

Salivary secretion has been reported to be lower in malnourished compared to healthy children (Table 2a). Agarwal et al. reported that saliva collection took longer (30–40 min) following stimulation with citric acid and strawberry flavor in malnourished children compared to control children or children (aged 1–10 years) with milder forms of PEM (10 min) [30]. Other research found impaired saliva flow rates in severely malnourished children (aged 8–12 years and 11–19 years) in both unstimulated and stimulated conditions [32,35]. Saliva flow rates were reported to be linked with level of malnutrition and the reduction in flow rate was related to the severity of PEM [35]. However, it should be noted, that malnutrition is often linked with dehydration which independently of malnutrition is known to affect saliva secretion rate [46,47].

#### 3.1.2. Saliva pH and buffer capacity

The pH of saliva was reported to be lower (6.9 ± 1.85) in underweight children compared to children of a normal weight (8.1 ± 1.95) (aged 6–12 years) [45] (Table 2b). In addition a reduction in salivary buffer capacity has been reported for this patient group [23,32,45].

#### 3.1.3. Saliva composition

Concentrations of sodium, potassium, phosphate, hexosamines, fucose, sialic acid and total protein as well as amylase activity in malnourished children have been reported to be similar to those of a control group (aged 8–12 years) [23] (Table 2c). However, in the malnourished group (aged 8–12 years) significantly lower concentrations of calcium and chloride as well as a decreased amount of protein secreted per minute were found in paraffin-stimulated whole saliva [23]. Agarwal et al. detected a continuous fall of protein, ferritin and arginase activity in stimulated saliva that correlated with the severity of PEM [30].

Analyses of unstimulated whole saliva show contradictory results regarding the concentrations of total IgA: while Johansson et al. detected no differences in the concentrations of total IgA between the PEM group and the control group; McMurray et al. found reduced IgA concentrations in malnourished children (aged 1.5–2 years) [23,31]. Salivary total protein, albumin and aminopeptidase were found in similar concentrations in all children by McMurray et al. and, Johansson et al. detected lower concentrations of anti-*S. mutans* IgA and lactoferrin as well as lower activity of the bacteria agglutinating protein (BAGP) in the PEM group.

#### 3.1.4. Oral mucosa integrity

PEM appears to have multiple effects on the oral tissues and oral disease development [35]. Besides deficiencies in protein malnourished children PEM results in a lack of a number of essential vitamins and minerals that effect structures in the oral cavity. These include folate and other B complex vitamins; vitamins A, C, and D, calcium and fluoride. Consequently, besides impaired dentition, the nutritional status of the body is also associated with disturbances in other oral structures and presents with recurrent aphthous stomatitis, atrophic glossitis, painful, burning tongue characterized by inflammation and defoliation of the tongue, mucosal atrophy and oral ulcers [35,48,49]. There is very little data reported on the extent to which oral mucosa integrity is impaired in malnourished children. However, there is evidence that long-term chronic malnutrition causes a significant reduction in resistance and progressive damage to the oral mucosa that will result in reduced resistance to colonization and invasion of pathogenic microorganisms [50] and consequently will most probably also enhance permeability and therefore oromucosal drug absorption.

In summary, the imbalance between the supply of the nutrients and the body's demand results in several oral manifestations that could alter oral drug absorption. However, whereas the impacts on dentition are usually irreversible, in children rehabilitation will most likely result in complete recovery of oral mucosa integrity, saliva secretion and composition.

### 3.2. Stomach

Volume, composition and physicochemical properties of gastric fluids are important factors regarding drug solubility and/or disintegration properties of solid oral dosage forms and thus can affect *in vivo* drug release. The motility pattern in the stomach and the secretion of gastric juices are directly dependent on food intake. Thus, it is necessary to differentiate between the fasted and fed state. Different nutrition habits or long periods of fasting lead to the assumption that gastric conditions in malnourished children may differ from conditions in healthy children, which may result in altered drug performance.

#### 3.2.1. Gastric contents

Several studies have shown correlations between reduced fasted gastric acid secretion and malnutrition (Table 3a). Gracey et al. detected, that unstimulated gastric acid secretion was reduced in 9 of 14 malnourished children, while maximal acid output (60 min after pentagastrin stimulation) was below normal in all malnourished patients (aged 7–54 months) [42]. Gilman et al. reported that the fasted gastric acid output was lower in severely malnourished Bangladeshi children compared to better nourished children (0.22 vs 0.52 mEq HCl/h) (aged 3.3 ± 2.4 years) [38]. In the children enrolled in the Gilman study, three weeks of nutritional rehabilitation lead to equivalent rates of fasted gastric acid secretion in the two groups showing that this is a reversible phenomenon [38]. At this point, it also should be noted that as for saliva secretion, impaired gastric secretion may relate to both malnutrition or dehydration of the children, which often cannot be clearly distinguished. Thus, the increase in gastric acid secretion could be also an effect of rehydration. Shashidhar et al. detected a decreased mean acid concentration in malnourished children (aged 12–60 months), here divided into kwashiorkor and marasmic children, under unstimulated and stimulated fasted conditions, although results show a high interindividual variability [51].

Under unstimulated fasted conditions the pH of gastric juice was above 4 in 76% of malnourished children; After nutritional rehabilitation this decreased to 69% in malnourished children compared to 55% in better-nourished children (aged 3.3 ± 2.4 years) [38]. Under stimulated conditions, the percentage of pH values above 4 was reduced: 26% in malnourished children, 24% in children after nutritional therapy and 0% in better-nourished children [38]. However, pH of gastric juice under stimulated fasted conditions is not equal to gastric pH under fed conditions. Thus, also the composition and quantity of food has an important impact on gastric pH, especially when considering that there are various types of diets worldwide.

Peptic activity was reported to be significantly reduced in malnourished children under fasted conditions compared to well-nourished children (aged 12–60 months) [51] (Table 3a). Yet, shortly after stimulation of gastric secretion peptic activity rose in all children although it was still significantly decreased in malnourished children.

The reduced gastric output observed at baseline in severely malnourished children correlates to a higher incidence of infections [53] credited to the loss of the gastric acid barrier. The relationship between *H. pylori* infection and acidity within the stomach is complex; a low level of acidity in the stomach may increase the risk of infection in the gastrointestinal tract and also overgrowth of intestinal bacteria that may lead to diarrhea. The prevalence of *H. pylori* in children is high in developing countries and since *H. pylori* infection is associated with an increased gastric pH, it might be associated with malnutrition [38,54,55].

**Table 3**
Gastric parameters.

*(a) Summary of data on changes in gastric contents*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Gracey et al., 1977 [42] | 14 Indonesian patients and 21 healthy controls<br>Age: 7–54 months | Wellcome classification: marasmus and kwashiorkor | Volumes were measured and the HCl content was estimated by titration to pH 7.4 | Basal gastric acid output was below normal in 4 of the 7 malnourished infants<br>In all malnourished patients maximal acid output was reduced compared to control group | Small study<br>No publication of measured values in control group |
| Gilman et al., 1988 [38] | 35 patients and 20 healthy controls<br>Age: 3.3 ± 2.4 years<br>Study was conducted in Dhaka, Bangladesh | NCHS (weight-for-height): marasmus, marasmic kwashiorkor and kwashiorkor | Volumes were measured and the HCl content was estimated by titration to pH 7.0 | Increased gastric pH in malnourished children compared to control group<br>Basal volume of gastric secretion was significantly lower in malnourished children compared to control group<br>Stimulated acid concentration and volume of gastric secretion was significantly diminished in malnourished children compared to control group | Small study<br>Well described study<br>Follow-up<br>Statistical analysis |
| Shashidhar et al., 1976 [51] | 30 patients and 12 healthy controls<br>Age: 12–60 months<br>Study was conducted in Baroda, India | Recommendation of Indian Academy of Pediatrics (1972): marasmus, kwashiorkor | pH meter and titrating with NaOH<br>Colorimetric method with haemoglobin | Reduced acid secretion/increased gastric pH in all malnourished children compared to control group<br>Reduced peptic activity in all malnourished children compared to control group | Small studyInclusion criteria of patients not comprehensible (recommendations of Indian Academy of Pediatrics)<br>Lack of information regarding the statistical test |

*(b) Summary of data on changes in gastric emptying*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Shaaban et al., 2004 [41] | 27 patients and 15 healthy controls<br>Age: 11.97 ± 6.03 months<br>Study was conducted in Cairo, Egypt | Wellcome classification: marasmus, marasmic kwashiorkor and kwashiorkor | Ultrasonographic examination | Delayed gastric emptying in marasmus and marasmic kwashiorkor patients compared to control group<br>Not statistically significant delay in gastric emptying of kwashiorkor patients compared to control group<br>Significantly faster gastric emptying after nutritional rehabilitation | Small study<br>Well described study<br>Follow-up<br>Statistical analysis |
| Franco et al., 1985 [33] | 9 patients and 7 healthy controls<br>Age: 5–29 months<br>Study was conducted in Ribeirão Preto, Brazil | Gomez index (weight-for-age): severely malnourished and [21] : kwashiorkor, marasmic kwashiorkor and marasmus | Double sampling technique with gastric tube | Volume of 5% glucose solution left in the stomach of children with marasmus were significantly lower than those observed in the controls at ten and 20 min after the beginning of the liquid meal<br>No difference between all children after nutritional rehabilitation and controls | Small study<br>Quality of method questionable<br>Patients treated with different helminthics such as thiabendazole, which can evoke unspecific gastrointestinal disorders<br>Follow-up<br>Statistical analysis |
| Franco et al., 1986 [34] | 22 patients and 7 healthy controls<br>Age: 7–45 months<br>Study was conducted in Ribeirão Preto, Brazil | Gomez index (weight-for-age): severely malnourished and McLaren: kwashiorkor, marasmic kwashiorkor and marasmus | Double sampling technique with gastric tube | No differences of gastric emptying between kwashiorkor patients and control group<br>Not statistically significant delay of gastric emptying of marasmic kwashiorkor patients compared to control group | Small study<br>Quality of method questionable<br>Patients treated with different helminthics such as thiabendazole, which can evoke unspecific gastrointestinal disorders<br>Follow-up<br>Statistical analysis |
| Brunser et al., 1990 [52] | – | – | – | Slow gastric emptying in malnourished children | Review<br>No reference indicated |

In conclusion, available literature reports reduced gastric acid secretion in malnourished children, yet nutritional rehabilitation seems to result in an immediate improvement. It should be noted that nutritional rehabilitation typically results in rehydration of malnourished children. Malnourished children with watery diarrhea are usually treated with Rehydration Solution for Malnutrition (ReSoMal) [56]. Hence the increase in gastric acid secretion can be caused by both nutritional rehabilitation and rehydration.

#### 3.2.2. Gastric emptying

Investigations on gastric emptying in malnourished children show contradictory results (Table 3b). Brunser et al. (within a review paper) stated without indicating a reference, that there are clinical observations showing that severe cases of malnutrition are characterized by gastric dilatation, slow emptying and vomiting [52]. Two studies investigating gastric emptying in marasmic, kwashiorkor and marasmic kwashiorkor children (aged 5–29 months and 7–45 months) showed that children with marasmus showed faster gastric emptying of a 5% (w/v) glucose solution administered at a volume of 20 mL/kg body weight compared to a control group. Severely malnourished children with kwashiorkor had no detectable abnormalities in gastric emptying, while in marasmic kwashiorkor children a tendency of delayed gastric emptying was observed [33,34]. However, the power of these studies is limited, as the patient group was treated with different helminthics such as thiabendazole, which can evoke unspecific gastrointestinal disorders. In contrast, a significantly delayed gastric emptying in both marasmic and marasmic kwashiorkor children (aged 11.97 ± 6.03 months) was reported by Shaaban et al. [41]. In an ultrasonographic study they investigated the impact of nutritional rehabilitation on gastric emptying using a liquid (infant powdered milk formula) and a semisolid meal (milk, rice and high protein additive). They found a clear delay in gastric emptying of both liquid and semisolid food in marasmic and marasmic kwashiorkor children when compared to a control group (aged 11.97 ± 6.03 months). As could be expected, the delay in the gastric half emptying time was higher with the semisolid than with the liquid meals [41]. Nutritional rehabilitation was observed to speed up gastric emptying after 30 ± 7 days of nutritional treatment [41].

### 3.3. Small intestine

The small intestine is the site where maximal drug absorption occurs. Therefore, small intestinal conditions, such as luminal contents, surface area, transit time and mucosal permeability, can affect drug absorption and this information can help to develop predictive *in vitro* test designs as accurately as possible.

#### 3.3.1. Small intestinal contents

The small intestinal contents influence the solubility of drugs which in turn will influence their absorption. Key components of small intestinal fluids are bile, enzymes and bacteria.

Mehta et al. analyzed the duodenal contents following a milk stimulus from sixty marasmic children between the ages of 9–42 months. Results showed significantly lower mean concentrations of conjugated bile acids (1.36 mg/mL vs. 2.92 mg/mL) and total bile acids in marasmic children compared to well-nourished children, while the concentration of free bile acids was increased (0.60 mg/mL vs. 0.06 mg/mL) (Table 4a). Unfortunately, measured pH values weren't published, but the low pH of duodenal juice was mentioned [43]. Duodenal aspirates were analyzed from 18 severely protein calorie malnourished children (aged 15–64 months) to measure the contents with respect to the ability to achieve micellar solubilisation of lipids. The results showed that micellar lipid and fat absorption were low in PCM children due to lower levels of bile salts [57]. Children under 5 years of age with severe acute malnutrition were shown to have higher total serum bile acids compared to controls which relates to lower biliary secretion within the GI tract [58].

Sauniere et al. analyzed the duodenal contents of 25 children (1 month to 8 years) with acute symptoms of kwashiorkor. Bicarbonate and volume of duodenal juice of malnourished children were not different compared to the normal African population, while pancreatic enzymes, such as amylase and lipase, were significantly decreased, except for trypsin, which was not affected [59]. These results agree with the findings from 40 children (aged 9–51 months) with kwashiorkor where a wide variation in significant depression of enzyme activity was observed [60] (Table 4b).

Underproduction of acid in the stomach is the most likely cause of the bacterial overgrowth observed in the small intestine of undernourished children. The impact of high levels of bacteria in the small intestine include impaired nutrient absorption and risks of sub-efficacious oral vaccination in children aged 2 months to 5 years [61]. Several studies have reported higher than usual levels of viable bacteria within the small intestine in malnourished children (aged 9 months to 6 years) [62,63] (Table 4c).

#### 3.3.2. Intestinal fluid output and dehydration in malnutrition

The adult small intestine receives large quantities of fluid via dietary fluid intake or as secretions from salivary glands, stomach, pancreas, liver and the small intestine itself. The small intestinal epithelium absorbs about 6–7 L of fluid per day. Only about 1.5 L enter the large intestine and are further reduced to less than 250 mL/day that are excreted with feces. If an individual has diarrhea then osmoregulation is affected and the fluid within the intestine is not reabsorbed and the total intestinal fluid output is elevated to balance the osmolality to favour the absorption [64]. The small intestine is typically a site of net water absorption which has been observed in children with malnutrition. However, in cases of malnutrition that is associated with diarrhea a net secretion of water was measured within the jejunum [65]. This alteration from net absorption to net secretion is likely to reduce the uptake of drugs within the GI tract in cases of diarrhea.

#### 3.3.3. Intestinal permeability

Several studies done in the 1960–1970s showed that the shape of the small intestinal wall changed from regular long villi in healthy patients (villi are structures within the small intestine that increase the small intestinal surface area and, consequently, absorption) to irregular broader and shorter villi in malnourished children (0–3 years) and that the shape in malnutrition is associated with an overall smaller surface area compared to healthy tissue [67,70,76] (Table 4e). However, increased permeation of cellular materials was seen suggesting that the intestine is more permeable in malnutrition [67,70,76]. As the severity of malnutrition increases so do the changes in the intestinal epithelium as the abnormalities in marasmus were mild in comparison to children (aged 0–3 years) with kwashiorkor [76]. Atrophy of villi in malnutrition has also been reported [68–70].

The Lactulose/Mannitol intestinal permeability test (L:M) is a commonly used technique to measure small intestinal function and can relate to changes in: (a) small intestinal epithelial area; (b) transcellular and paracellular transport and (c) damage and permeability. Mannitol can be used as a marker to assess the mucosal absorptive area and lactulose to assess the integrity of the intestinal membrane. In some studies a lactulose/rhamnose test is used; rhamnose is similar to mannitol in that it is a monosaccharide and mucosal damage will reduce mannitol/rhamnose absorption whilst increasing permeability of lactulose.

A typical reference value for L:M is 0.09 as this was defined as an upper normal limit in 30 healthy Dutch children (aged 0–16 years) [77]; values greater than 0.09 suggest enteropathy is present. Typically, lactulose (which is large) relates to the overall integrity of the membrane and mannitol can relate to the surface area or overall absorptive capacity of the membrane.

A study on 97 severely underweight Bangladeshi children (mean age

**Table 4**
Small intestinal parameters.

*(a) Bile concentrations*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Mehta et al. (1984) [43] | 60 patients and 15 controls (normal age-matched)<br>Age: 9–42 months<br>Study conducted in Rohtak, India | Gomez index < 60% of weight for age standard | Analysis of duodenal aspirates for free and conjugated bile acids by thin-layer chromatography | Mean concentration of conjugated bile acids as well as total bile acids was significantly lower in marasmic children compared to normal age-matched children<br>The concentration of free bile acids was significantly higher in marasmic children compared to normal age-matched children | Small study<br>Statistical analysis |
| Schneider and Viteri, 1974 [57] | 18 patients with severe PCM aged 15–64 months and 4 controls (healthy children aged 17–23 months) | Weight for height (76% for PCM children) | Analysis of duodenal aspirates for bile acids | Lower levels of conjugated bile acids (3.07 in PCM + diarrhea; 8.28 in PCM – diarrhea compared to 10.96 μM/mL in controls) yet higher levels of free bile acids (1.68 in PCM + diarrhea; 0.78 in PCM – diarrhea compared to 0.62 μM/mL in controls) | Small sample population<br>Statistical analysis |
| Redmond et al. (1972) [62] | 20 patients with kwashiorkor and 10 controls (children with gastro-enteritis)<br>Age: 3–24 months<br>Study conducted in the South African Medical Research Council Clinical Nutrition Research Unit at the University of Cape Town and the Red Cross War Memorial Children's Hospital | Kwashiorkor stated, but definition not stated | Analysis of duodenal aspirates for bile acids | Free bile acids were detected in 8/20 patients with Kwashiorkor and 2/10 with gastro-enteritis (the control group) | Very small study<br>No statistical analysis |

*(b) Enzyme concentrations*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Sauniere et al. (1986) [59] | 11 patients (from the Ivory Coast) with Kwashiorkor and 23 controls (French children)<br>Age: 1 month to 8 years | Not stated | Analysis of duodenal aspirates | A decrease in lipase, amylase, chymotrypsin and phospholipase was found in children with Kwashiorkor compared to the control group | Small sample population<br>Statistical analysis |
| Thompson and Trowell, 1952 [60] | 40 patients aged 12–51 months and 24 controls aged 9–51 months (in patients without diagnostic criteria for kwashiorkor)<br>Study conducted at Mulago Hospital and the Department of Medicine, Makerere College, Kampala, Uganda | "Established kwashiorkor" | Analysis of duodenal aspirates | A reduction in the concentration of amylase and lipase in children with Kwashiorkor compared to the control group | Small sample population<br>Statistical analysis |

*(c) Bacteria*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Omoike and Abiodun, 1989 [66] | Nigerian children aged 2 months to 5 yearsWell-nourished diarrhea-free Nigerian children were controls compared to<br>(i) well-nourished children with acute diarrhea and (ii) malnourished children with or without diarrhea<br>50 children in total | Well-nourished vs kwashorkor; marasmus; marasmic kwashiorkor +/- diarrhea | Analysis of duodenal aspirate | Higher levels of bacteria were found in the small intestine of malnourished children<br>Well-nourished children had bacterial counts < $10^5$ organisms/mL<br>In malnourished children counts were $10^3$–$10^9$ organisms/mL | Small sample population<br>Statistical analysis |
| Heyworth and Brown, 1975 [63] | Gambian children aged 9–34 months (n = 25)<br>Those with chronic diarrhea were compared to those with acute diarrhea | Marasmus; Kwashiorkor; marasmic kwashiorkor | Analysis of duodenal aspirate | Significantly higher levels of bacteria (> $10^5$ organisms/mL) were found in the small intestine of 22/25 malnourished children<br>Chronic diarrhea is associated with increased levels of bacteria | Small sample population<br>Statistical analysis |

(*continued on next page*)

**Table 4** (*continued*)

*(c) Bacteria*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Mata et al. (1972) [67] | 13 patients with acute PCM and 4 controls (normal)<br>Age: 1–6 years<br>Study conducted in Clinical Center of the Institute of Nutrition of Central America and Panama | PCM characterized by a marked growth retardation | Analysis of gastric, duodenal and jejunal aspirates | Those with malnutrition plus diarrhea showed higher levels of bacteria in their stomach and jejunum yet there was no difference for those with malnutrition (without diarrhea) compared to controls | Small sample population<br>No statistical analysis |

*(d) Shape of intestinal epithelium*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Campbell et al. (2003) [68] | 38 Gambian patients and 19 age-matched UK controls<br>Age: 0–3 years | Weight z score, height z score and BMI z score | Biopsy taken and microscopic analysis of villous height and crypt depth | Villous/crypt ratio was 0.80 in Grade 1 PEM; 0.84 in grade 2 PEM; Gambian controls had villous/crypt ratio of 0.81 yet in UK controls the ratio was 2.1 | Small sample population<br>Statistical analysis |
| Farràs et al. (2018) [69] | 15 Zambian patients with persistent diarrhea<br>Mean age 15 months | WHO Child Growth Standards | Biopsy taken and microscopic analysis of villous height and crypt depth | Clear evidence of villous blunting and shorter villus height compared to literature controls | Small study, no controls<br>No statistical analysis |
| Burman et al. (1965) [70] | 17 children < 3 years from Nairobi with kwashiorkor and children from England as controls | Kwashiorkor | Jejunal biopsies | The jejunal tissue showed more ridges and fewer fingers in children with Kwashiorkor compared to controls | Small study with biopsies |

*(e) Changes in intestinal permeability*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Hossain et al. (2016) [28] | 925 children aged 13.2 ± 5.2 months from a Bangladeshi slum | WHO (Weight for age; height for age; weight for height; mid-upper arm circumference) | Lactulose/Mannitol intestinal permeability test (L:M) | 44% had enteropathy (leaky membrane) as reflected by a L:M of ≥0.09 Younger age and having diarrhea increased the risk factors for having enteropathy | Robust methodology<br>Large population<br>Well described study |
| Brewster et al. (1997) [71] | 149 children aged 26.7–29.9 months with Kwashiorkor and 45 inpatient controls in Malawi | Kwashiorkor | Lactulose/Rhamnose intestinal permeability test (L:R) L:R test | The initial geometric mean L-R ratios (×100) (with 95% confidence interval) in kwashiorkor were 17.3 (15.0 to 19.8) compared with 7.0 (5.6 to 8.7) for controls | Robust methodology<br>Large population<br>Well described study |
| Goto et al. (1999) [72] | 158 Guatemalan infants < 12 months from low-income, periurban community of Guatemala City | Length for age; weight for age; weight for length | Lactulose/Mannitol intestinal permeability test (L:M) | 30% had leaky intestinal permeability (L:M ≥ 0.07)<br>The L:M in currently asymptomatic infants who had diarrhea during the week before testing (0.087; CI = 0.49, 0.154) was higher (0.087) than that in children who had been free from diarrhea for at least 1 week (0.052).<br>Younger age and having diarrhea increased the risk factors for having enteropathy | Robust methodology<br>Large population<br>Well described study |
| Behrens et al. (1987) [40] | 68 Gambian infants aged 0–18 months | Marasmus with weight for age at < 60% | Lactulose/Mannitol intestinal permeability test (L:M) | Those with marasmus had significantly higher L:M compared to others<br>L:M ratio was 1.3 in malnourished population compared to 0.42 in well nourished children and 1.0 in children with chronic or acute diarrhea | Good statistical analysis and follow-up |
| Lunn et al. (1991) [73] | 119 Children from 2 to 10 months in Gambia | Height and weight | Lactulose/Mannitol intestinal permeability test (L:M) | The L:M ratio could predict 43% of the observed variation in length and 39% of the observed variation in weight growth<br>This shows that growth is related to intestinal permeability where enteropathy limits growth | Statistically strong study |
| Campbell et al. (2003) [68] | 73 children aged 8–48 weeks from rural Gambia | Height and weight | Lactulose/Mannitol intestinal permeability test (L:M) | Higher permeability reported to correlate to the severity of malnutrition | Robust study<br><br>Robust study |

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**Table 4** (*continued*)

*(e) Changes in intestinal permeability*

| Reference | Population | Malnutrition definition used | Methodology | Findings | Quality of the study |
|---|---|---|---|---|---|
| Boaz et al. (2013) [26] | 26 south Indian children aged 6–59 months hospitalized for management of acute gastroenteritis plus 20 controls | Malnutrition was defined as a weight for age Z score<br>Below −2SD by WHO | Lactulose/Mannitol intestinal permeability test (L:M) | 61.5% of children with malnutrition and acute diarrhea and 32.2% of children without diarrhea had increased intestinal permeability | |
| Hossain et al. (2010) [27] | 77 children 13.1 ± 4 months severely malnourished Bangladeshi children and 17 aged match controls | weight-for-age Z-score (WAZ) < −3 in relation to the WHO 2006 standard | Lactulose/Mannitol intestinal permeability test (L:M) | Eighty-four percent of the children had L/M ≥ 0.07, suggestive of impaired intestinal functionThe L:M ratio of malnourished children was greater (0.09) compared to controls | Robust study |
| Manary et al. (2010) [74] | 25 asymptomatic Malawian children aged 3–5 years risk for tropical enteropathy and zinc deficiency | Weight and height | Lactulose/Mannitol intestinal permeability test (L:M) | 88% of children had abnormal L:M ratio (> 0.10)<br>L:M was directly correlated with endogenous faecal zinc and negatively correlated with net zinc retention | Robust study |
| Johansen et al. (1989) [75] | Children aged 1 month to 3 years (well nourished (n = 17) and severely malnourished (n = 9)) | < < 60% standard weight for age | Absorption of polyethylene glycols (PEG) from 292 to 1250 Da<br>Measured by determination in urine | Reduction in permeability of PEGs was observed in severely malnourished children<br>Diarrhea exacerbated this effect | Good methodology |

L:M test: Lactulose/Mannitol intestinal permeability test. L:R test: Lactulose/Rhamnose intestinal permeability test.

9 years) showed that the difference in mannitol absorption was greater than in lactulose absorption in malnourished children compared to healthy children; this relates to the loss of surface area which is consistent with the shape changes in the villi [27]. Intestinal biopsy studies [70,78] in malnourished children show that kwashiorkor is associated with villous atrophy, decreased villous-crypt ratio and increased cellularity of the lamina propia; these changes impact the absorptive capacity as well as the overall surface area. Several studies have been conducted to investigate the intestinal permeability of malnourished children with or without diarrhea as well as before and after nutritional rehabilitation [26–28,39,40,71,79]. The damaged villi lead to a compromised intestinal wall that can be associated with absorption of large macromolecules that lead to immune- and inflammatory diseases. These diseases further damage the epithelial wall and reduce the barrier for absorption of drugs. Chronic intermittent diarrhea may be linked to carbohydrate malabsorption within the intestine due to the rapid intestinal transit times associated with diarrhea that may limit overall absorption in addition to the differences in the permeability across the membrane [76]. Brewster et al. showed that the combination of increased lactulose permeation and decreased L-rhamnose absorption results in a higher prevalence of diarrhea [71]. Behrens et al. found repeatedly increased intestinal permeability to disaccharides in a number of tests on 68 Gambian infants (aged 0–18 months), most of whom had at least one episode of diarrhea [40]. These findings lead to the conclusion that diarrhea is associated with mucosal damage, which results in compromised small intestinal barrier function and uptake of larger molecules, such as lactulose, through the site of damage [73]. Therefore, diarrhea seems to correlate with abnormally high L/R – ratios and thus with an increased intestinal permeability. Indeed, L/R – ratios of patients with diarrhea were observed to be above normal in several studies and correlated with the duration and frequency of diarrheic events and returned to normal with resolution of diarrhea [26,40,71]. It can be stated that malnutrition itself is associated with changes in the intestinal mucosa resulting in a reduced absorptive area and malabsorption, while diarrhea, which is often linked to malnutrition, is associated with mucosal damage.

Estimates of the prevalence of impaired intestinal permeability (higher values of L:M) range from 62 to 96% that results in poor growth among infants and young children in developing countries in sub-Saharan Africa and Asia (urinary L:M concentration ratio > 0.10–0.12) [36,74,80]. Perturbed intestinal function is associated with the malabsorption of macro- and micronutrients, including fat, carbohydrates, and vitamins A, B12 and folate [81–83]. Wessells et al. (2013) study looked at zinc absorption in Burkinabe children (6–23 months) and also measured the lactulose/mannitol measures to assess intestinal integrity. The results showed that the absorption of zinc was linked to the L:M permeability test with a greater proportion of normal children showing higher levels of zinc absorption, however this was only significant different for the most severely affected children [29].

### *3.3.4. Intestinal transit time*

The transit time through the small intestine is an important factor regarding the absorption of nutrients and drug products, as it affects the time that food and drugs have contact with the absorptive epithelium. In 1999 there was one study conducted regarding orocecal transit time in malnourished children. Myo-Khin et al. [37] used the lactulose breath hydrogen test to investigate orocecal transit in 90 Myanmar children between the ages of 1 and 5 years. After classification according to weight-for-age, length-for-age and weight-for-length indices, 31 children were defined to be malnourished, whose orocecal transit time was compared to transit time in well-nourished children. No significant difference between malnourished and well-nourished children was found. However, children with a history of diarrhea were excluded from the study. As diarrhea and vomiting are two of the most common problems of PEM, as subsequent symptoms, a reduced retention of drugs and decrease of the transit time through the bowel can be

**Table 5**
Potential impacts of specific features on oral drug absorption in malnourished children.

| Gastro-intestinal region | Impact in malnourished children | Consequences for oral drug absorption |
|---|---|---|
| Oral cavity | Reduced saliva secretion | Impaired disintegration/dissolution of orally disintegrating dosage forms and swallowing |
| | Reduced saliva pH<br>Reduced saliva buffer capacity<br>Reduced saliva protein and enzyme levels | Limited impact on oral drug absorption |
| | Impaired oral mucosa integrity | Increased chance for oromucosal drug absorption |
| Stomach | Increased gastric pH/reduced acid secretion | Limited dissolution of (weakly) basic drugs may limit bioavailability |
| | Reduced peptic activity | Increased plasma levels of drugs that are prone to enzymatic degradation |
| | Unknown impact on gastric emptying (yet compromised in vomiting/diarrhea) | Risk of an increased variability in plasma profiles |
| Small intestine | Reduced bile acid concentrations | Reduced ability to solubilize poorly soluble drugs; may reduce overall bioavailability |
| | Reduced enzyme activity | Limited impact on drug absorption except in cases where prodrugs, that require enzymatic cleavage, are used |
| | Increased permeability | Enhanced absorption of certain drugs due to increased permeability; increased bioavailability may lead to toxicity or the need for dose titration |
| | Reduced surface area | Reduced area for overall absorption may reduce overall bioavailability, particularly in cases of diarrhea |
| Colon | No evidence found | Unknown |

expected [13].

### 3.4. Colon

No literature was identified that reported colonic transit time and colonic permeability in malnourished subjects. There are some studies suggesting that malnutrition is a risk factor for an increased incidence or duration of diarrhea [84–87]. As a consequence of diarrhea, colonic transit time in malnourished children might be shorter than in healthy children. However, some of the currently available reports on this topic are contradictive and the information available to date is not sufficient for a final conclusion. Another important point to consider in this discussion would be the alterations in the gut microbiome that are reported for severely malnourished children [88]. Future research should thus focus on expanding the knowledge in this field.

## 4. Discussion

Malnutrition can affect the gastrointestinal tract and subsequently, modify drug absorption. Therefore, malnutrition can have an indirect impact on drug toxicity or suboptimal therapeutic effects. Clearly, there is a pressing need to understand the impact of malnutrition in drug absorption.

Table 5 summarizes the findings from the literature and provides some implications for drug absorption in malnourished children.

The data identified within this search was generally quite old. Some general trends towards alterations in oral, gastric and small intestinal physiology were identified. Next to no information on the colon, another vital section of the GI tract, was available. There is very limited novel data available to really understand the implications of malnutrition on the absorption of orally administered medicines, yet this can be of great importance for such a vulnerable population. A systematic review on the impact of malnutrition on the pharmacokinetics of drugs used in children reported that the extent of absorption was increased in 8 drugs, yet this was attributed to be likely due to changes in clearance rather than the GI physiological changes [14]. However, these statements should be handled with care, since these 8 drugs had significantly different properties with regard to molecular weight, aqueous solubility and permeability in adults and represented candidates from all classes of the biopharmaceutics classification system (BCS). Consequently, at least for some of these APIs plasma levels in malnourished children are likely to be affected by GI physiology. Moreover, for several other compounds, examples where absorption in malnourished children was unchanged or reduced can be found in the literature [15–18].

Current *in vitro* tools that are used to predict oral drug absorption are based on adult physiologies and Western populations. The simulated gastrointestinal media and biorelevant dissolution methods available to date address GI conditions in fasted and fed healthy European subjects [89–93]. Biorelevant *in vitro* tools addressing the particular GI features in malnourished children are currently unavailable. Therefore, there is a real need to develop biorelevant *in vitro* methods that reflect the conditions found in malnourished children and different types of malnutrition to better understand how drugs are absorbed in these critical and vulnerable populations. This will ensure the selection of adequate doses ensuring a safe and effective drug treatment of these children.

Biorelevant *in silico* tools using physiologically based pharmacokinetic modelling can provide a tool to better understand the disposition of drugs within a range of populations. There has been some work looking at simulating a malnourished population to explore drug pharmacokinetics [94]. *In silico* tools permit exploration of predicted pharmacokinetics when considering each different aspect of GI physiology/anatomy for the population under investigation which can provide details on sensitivity to change based on the type of drug presented. Further work is required in this area.

## 5. Conclusions

Despite the significance of malnutrition as a global health issue this population has been neglected when considering efficacy of medicines used to treat malnourished children. Oral drug treatment during the acute phase of malnutrition needs to be carefully considered to ensure that the therapy is efficacious. Further work is required to develop biorelevant models that incorporate the findings from this review and to verify these *in vitro* and *in silico* models using appropriate pharmacokinetic data. All methods need to acknowledge the heterogeneity of malnutrition as a disease state as well as the age-related changes associated with paediatric populations.

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