BACKGROUND

Obesity is a major risk factor for type 2 diabetes. Among individuals with type 2 diabetes, but also among those with type 1 diabetes, obesity is strongly associated with the development of chronic kidney disease. Indeed, diabetes is the most prevalent comorbidity among individuals with chronic kidney disease initiating renal replacement therapy in developed countries, reportedly developing in approximately 50% of people with type 2 diabetes. The Status of Nutrition In Hemodialysis Patients Survey (SNIPS), a large, representative sample of Israelis on haemodialysis, identified elevated malnutrition risk among people with versus without diabetes.

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Abstract

Background: Increased malnutrition risk has been observed in more than 40% people on haemodialysis in Israel. It is not clear that this risk is homogeneously distributed among people with versus without diabetes.

Objectives: To examine the influence of diabetes on malnutrition risk among people on haemodialysis.

Methods: This cross-sectional study included a representative sample of 375 individuals on haemodialysis treated in hospital dialysis centres throughout Israel. Of these, 126 had diabetes. Dietary intake, biochemistry, anthropometric and hemodynamic measures were recorded. Malnutrition risk categories were defined: “minimal”: body mass index (BMI) ≥23 kg/m2 and serum albumin ≥38 mmol/L; “mild”: BMI <23 kg/m2 and albumin ≥38 mmol/L; “moderate”: BMI ≥23 kg/m2 and albumin <38 mmol/L; “severe”: BMI <23 kg/m2 and serum albumin <38 mmol/L. These categories were dichotomized to “minimal” versus elevated malnutrition risk.

Results: Despite greater BMI, elevated malnutrition risk was identified in 58.8% of individuals with versus 39.3% without diabetes. Adherence to International Society for Renal Nutrition and Metabolism nutrition guidelines was poor regardless of diabetes status. In multivariable logistic regression analysis, diabetes: OR 2.15; C-reactive protein (nmol/L): OR 1.02; delivered dialysis dose (Kt/V): OR 6.07; and haemoglobin (g/L): OR 0.79, predicted elevated malnutrition risk, even after controlling for age, sex and years on haemodialysis.

Discussion: Individuals on haemodialysis who have diabetes have elevated malnutrition risk compared to those without diabetes despite greater BMI.

Keywords
diabetes, diet and nutrition, epidemiology, haemodialysis, obesity
malnutrition risk in more than 40% of the study population. Elevated malnutrition risk was associated with the presence of major comorbidities; reduced haemoglobin; elevated C-reactive protein; and need for feeding assistance. In that study, malnutrition risk was defined as BMI <23 kg/m² and/or serum albumin <3.8 g/L, thus capturing depletion of both somatic and visceral protein stores and permitting the inclusion of heavier individuals, many of whom have diabetes, a group previously excluded from the malnutrition risk definition. This definition contrasts with that of the International Society for Renal Nutrition and Metabolism (ISRN), which requires the presence of abnormalities in three of the four following areas: serum chemistry measures, body mass, muscle mass measures and/or dietary.

It seems, however, that the ISRN definition might underestimate malnutrition risk in individuals with type 2 diabetes, due to the association between this comorbidity and weight loss inhibition. BMI is often elevated in people with diabetes, including those on haemodialysis. Nevertheless, BMI is inversely associated with mortality and hospitalization in people on haemodialysis, in contrast to the association between elevated BMI and adverse outcomes in the general population. These studies often omit dietary intake when studying these associations, making it difficult to assess whether poor dietary intake and its accompanying increase in malnutrition risk are masked by elevated BMI.

The present study compares nutrition risk between individuals with versus without diabetes among members of the SNIPS cohort. The percentage of individuals meeting ISRN nutrition recommendations for the intake of energy, protein, sodium and phosphorus, was also compared by diabetes status.

2 | METHODS

2.1 | Overall study design and plan

Status of Nutrition In Hemodialysis Patients Survey: SNIPS was a national, multi-centre, cross-sectional survey designed to estimate malnutrition risk in a large, representative sample of Israelis on haemodialysis treated at hospital centres. Additionally, SNIPS assessed the percentage of people meeting ISRN nutrition recommendations for the intake of energy, protein, sodium and phosphorus. Data were collected from 2013 to 2016.

2.2 | Study population

A representative sample of the Israeli haemodialysis population treated in hospital centres was recruited. Each centre stratified its population by age, sex, ethnicity, years of dialysis and any diabetes (yes/no). Subjects were randomly selected for participation from within each stratum, the number from each stratum proportionate to the target population at each centre.

2.3 | Inclusion criteria

Israelis on haemodialysis were eligible for participation in SNIPS if they received haemodialysis treatment at a participating hospital centre in Israel and if they agreed to enrolment. All individuals received their usual care from their hospital haemodialysis team.

2.4 | Exclusion criteria

Individuals on haemodialysis with active malignancy and those receiving total parenteral nutrition or who were fed through a gastrostomy or jejunostomy tube were excluded from participation in SNIPS.

2.5 | Informed consent

All interested individuals received a detailed, informed consent sheet explaining the purpose of the study and possible benefits from knowledge gained. All individuals provided signed informed consent prior to inclusion in the study. The study was approved by the Institutional Ethics Committee (Helsinki Committee) at each participating centre and by the Israel Ministry of Health.

2.6 | Dietary intake

Food intake was assessed using a standard, multi-pass, five-step 24-hour recall. This method involves a face-to-face
structured interview, which the interviewer records by hand. The first pass is an unstructured “quick list” in which the respondent reports all food consumed from midnight to midnight on the day prior to the interview. In the second pass, the investigator queries food intake between meals. The third pass expands upon information gathered during the first pass, querying cooking method, portion size and specific ingredients. In the fourth pass, the interviewee refers to a list of frequently forgotten foods including alcohol, beverages, snacks and dietary supplements. The 24-hour recalls were performed by registered dieticians or physicians who had been trained in the data acquisition method. Variability was reduced by having interviewers undergo simulations to rehearse and standardize the dietary intake method. Variability was further reduced by having a single registered dietician analyse all 24-hour recalls. Dietary intake was analysed using “Tzameret” Nutrition Analysis software (Israel Ministry of Health), which utilizes an Israeli nutrition database. Macronutrients and the following micronutrients were analysed: vitamin A; beta carotene; thiamin; niacin; riboflavin; vitamin B6; vitamin B12; folic acid; vitamin C; vitamin D; vitamin E; calcium; iron; phosphorus; potassium. Also assessed was adherence to ISRN Nutrition Recommendations for energy, protein, sodium and phosphorus, are as follows: energy: 30–35 kcal/kg/day; protein: 1.2–1.4 g/kg/day; sodium: 80–100 mmol/day; and phosphorus, 800–1000 mg/day.

2.7 | Demographics, Medical History, Laboratory Values

Demographic data, medical history and prescribed medications and supplements were extracted from medical records closest to the day on which the 24-hour recall was performed. Blood chemistry, lipid profile, parathyroid hormone (PTH), complete blood count and delivered dialysis dose (Kt/V) were recorded from the monthly medical evaluation proximal to the date of the 24-hour diet recall.

2.8 | Definitions

2.8.1 | Malnutrition Risk

The ISRNM defines malnutrition using biochemical, body weight, muscle mass and dietary intake measures, requiring the presence of at least three of the four criteria. The body weight criteria, which specifies BMI<23 kg/m²; total body fat <10%, or unintentional weight loss of 5% over 3 months or by 10% over 6 months, may be excessively restrictive for people on haemodialysis, excluding those with normal or even elevated body weight who preserve BMI through insulin resistance or other mechanisms, yet have other features of malnutrition. We thus categorized malnutrition risk into the following four categories: “minimal” if BMI ≥23 kg/m² and serum albumin ≥38 mmol/L; “mild” if BMI <23 kg/m² and serum albumin ≥38 mmol/L; “moderate” if BMI ≥23 kg/m² and serum albumin <38 mmol/L; and “severe” if BMI<23 kg/m² and serum albumin <38 mmol/L. This definition identified elevated malnutrition risk in almost 50% of individuals on haemodialysis, including those with normal or elevated BMI.

2.9 | Diabetes, Overweight and Obesity

To reduce variability, body weight was calculated as the mean of three post-dialysis measures, one on the day of the 24-hour recall and the two post-dialysis measures immediately preceding it. Height was recorded to the nearest 0.5 cm. BMI was calculated as weight (kg)/height (m²). Ideal body weight (IBW) was defined 0.9*H(cm)- 88 in men and 0.9*H(cm)-92 in women. Diabetes was defined as the presence of the diagnosis in the medical record, and people were categorized by diabetes (yes/no). Because diabetes is strongly associated with overweight/obesity, the three SNIPS cohort members with BMI<18.5 kg/m² were removed from the analysis. Of these, one had diabetes and two did not. Thus, a total of 375 people were included in the present analysis.

2.10 | Sample Size

The present report includes 375 individuals, omitting the three individuals with BMI <18.5 kg/m². In the present study, which aimed to compare malnutrition risk by diabetes status, a sample size of 120 individuals in each group (people with diabetes, people without diabetes) provides 80% power to detect a true, between group difference of 18% in the prevalence of any increased malnutrition risk. In fact, there were 126 individuals with and 249 without diabetes, which provides approximately 82% power to detect the stated endpoint.

2.11 | Data Analysis

All statistical analyses were performed on SPSS v. 25.0 (IBM Inc., USA). Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Distributions of the following continuous variables did not differ from normal: delivered dialysis dose (Kt/V); creatinine; mean systolic blood pressure; blood calcium; the
calcium-phosphorus product; and % of kcal provided by each of the macronutrients. All other continuous variables had distributions deviating from normal. Categorical variables such as diabetes (yes/no) and comorbidities were described using frequency counts and expressed as n (%). Continuous variables were described as mean ± standard deviation and compared by diabetes status using the two-sample t-test or the Mann-Whitney test for those variables with a distribution that deviated significantly from a normal distribution. Associations between categorical variables were assessed using the chi-square test. Categories of malnutrition risk were collapsed so that minimal malnutrition risk was compared to any elevation in malnutrition risk (mild, moderate and severe). Logistic regression analysis was used to model this dichotomized malnutrition risk status variable. To develop that model, variables were compared by malnutrition risk status. All variables found to be associated with malnutrition risk status were entered into the initial model and the variables in the final model was selected using a backward, stepwise approach. Age, sex and years on haemodialysis were forced into the final model because of their potential to confound associations with malnutrition risk status. All tests are two-sided and considered statistically significant at p < 0.05.

3 | RESULTS

Of the 375 SNIPS cohort members included in this analysis, 126 (33.6%) had diabetes, of whom 7 (5.6%) had type 1 and the rest had type 2 diabetes. Characteristics of the study population are presented by diabetes status in Table 1. People with diabetes have been on dialysis for fewer years than people without diabetes. Among people with diabetes, a smaller percentage was comprised of women while a greater percentage was composed of Jewish people (vs. any other ethnic group). A greater percentage of people with diabetes had difficulty chewing and/or swallowing, though the percentage of people who needed feeding assistance did not differ by diabetes status. Not surprisingly, hypertension and cardiovascular disease were more prevalent in people with diabetes. Malnutrition risk also differed by diabetes status. A smaller percentage of people with diabetes had minimal malnutrition risk, and almost twice the percentage had moderate malnutrition risk, defined as BMI ≥ 23 kg/m² but albumin < 38 mmol/L. When malnutrition risk was dichotomized to minimal malnutrition risk versus any elevation in malnutrition risk (mild, moderate or severe), and this was compared by diabetes status, a greater percentage of individuals with than without diabetes were at elevated malnutrition risk: 58.7% versus 39.4%, p < 0.001.

Table 2 presents blood, hemodynamic and anthropometric measures by diabetes status. As expected, glucose and triglyceride levels were higher in people with versus without diabetes. Serum albumin was lower in people with diabetes, suggesting depletion of visceral protein stores. Nevertheless, BMI and % of ideal body weight were greater among people with diabetes, though people both with and without diabetes were overweight. Both mean systolic and diastolic blood

| TABLE 1 | Characteristics of the study population by diabetes status (yes/no) |
|-----------------|------------------|------------------|-----------------|
| **Characteristic** | **Diabetes** N = 126 | **No Diabetes** N = 249 | **p-value** |
| Age (years)a | 66.5 ± 9.7 | 63.5 ± 14.3 | 0.17 |
| Sex (% women) | 55 (43.7) | 140 (56.2) | 0.02 |
| Years of dialysisa | 1.7 ± 3.9 | 3.0 ± 5.6 | 0.02 |
| Present smoking | 9 (7.1) | 18 (7.2) | 0.98 |
| Jewish | 83 (65.9) | 136 (54.6) | 0.04 |
| Family status | | | 0.003 |
| Married | 98 (77.7) | 149 (59.8) | |
| Widowed | 18 (14.3) | 36 (14.5) | |
| Divorced | 7 (5.6) | 36 (14.5) | |
| Single | 3 (2.4) | 28 (11.2) | |
| Resides at home | 126 (100.0) | 241 (96.8) | 0.15 |
| Requires feeding assistance | 7 (5.6) | 9 (3.6) | 0.38 |
| Difficulty chewing/swallowing | 9 (7.1) | 4 (1.6) | 0.006 |
| Comorbidities | | | <0.001 |
| Hypertension | 97 (77.0) | 105 (42.2) | |
| Cardiovascular diseaseb | 64 (50.8) | 54 (21.7) | <0.001 |

Malnutrition riska

| Status | Minimal: BMI≥23 kg/m² and albumin ≥38 mmol/L | Mild: BMI<23 kg/m², albumin ≥38 mmol/L | Moderate: BMI≥23 kg/m², albumin <38 mmol/L | Severe: BMI<23 kg/m², albumin <38 mmol/L |
|-----------------|------------------|------------------|-----------------|-----------------|
| N | 52 (41.3) | 3 (2.4) | 65 (51.6) | 6 (4.8) |
| | 151 (60.6) | 11 (4.4) | 69 (27.7) | 18 (7.2) |

Distributions of continuous variables deviated from normal, so were compared by diabetes status using the Mann-Whitney U test. Nominal variables were compared by diabetes status using the chi square test.

aData presented as mean ± standard deviation; otherwise, data are presented as n (%)
bCardiovascular disease = history of one or more of the following indicated in the medical record: coronary heart disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft); stroke; peripheral vascular disease (intermittent claudication, amputation).
Dietary intake is presented by diabetes status in Table S2. Dietary intake did not differ by diabetes status for any of the nutrients measured.

Table 3 presents the percentage of individuals meeting International Society for Renal Nutrition and Metabolism (ISRN) dietary recommendations for people on haemodialysis, by diabetes and nutrition risk status. Only a minority of people in both groups met ISRN dietary recommendations. More people with than without diabetes met the requirements for sodium intake (p = 0.006). Energy intake, protein intake and dietary phosphorus intake did not differ by diabetes. A greater percentage of people with elevated malnutrition risk met ISRN dietary guidelines for energy intake than those with minimal malnutrition risk. The percentage of individuals meeting the ISRN recommendations for protein, sodium or phosphorus did not differ by malnutrition risk status.

Characteristics differing by dichotomized malnutrition risk (minimal vs. mild, moderate or severe) are presented in Table S3. BMI and serum albumin were not included since they form the definition of malnutrition risk. Interestingly, age, kcal intake and years on haemodialysis did not differ by malnutrition risk.

Table 4 presents the multivariable logistic regression analysis of elevated malnutrition risk. Diabetes emerged as a statistically significant predictor of elevated malnutrition risk, more than doubling the odds of this outcome (OR 2.15, 95% CI 1.35–3.43). Every 1 (mmol/L) increase in C-reactive protein, a marker of inflammation, increased odds of elevated malnutrition risk by 2% (OR 1.02, 95% CI 1.00–1.03). Each 1-unit increase in the delivered dialysis dose increased odds of elevated malnutrition risk by 2% (OR 1.02, 95% CI 1.00–1.03). Each 1-unit increase in the delivered dialysis dose increased odds of elevated malnutrition risk by more than sixfold (OR 6.07, 95% CI 1.89–9.53). On the other hand, each 1 g/L increase in haemoglobin reduced the odds of elevated malnutrition risk by 21% (OR 0.79, 95% CI 0.66–0.94). Age, sex and years on haemodialysis did not contribute to the model but were forced in to control for their potential confounding effect. The regression was statistically significant (p < 0.001).

4 | DISCUSSION

The present study demonstrates that malnutrition risk categories are not similarly distributed by diabetes status; specifically, more people with than without diabetes had moderate malnutrition risk. When malnutrition risk was dichotomized, almost 60% of people with diabetes had elevation of malnutrition risk compared to almost 40% of people without diabetes. This is somewhat surprising because people with diabetes had greater BMI than people without diabetes.

Malnutrition has been described among overweight and obese individuals, typically characterized as various micronutrient deficiencies associated with consuming a highly refined diet.17 It has been suggested that one mechanism...
explaining the association between overweight/obesity and type 2 diabetes is micronutrient deficiencies, including thiamine, vitamin C and B12. In the present study, however, differences in micronutrient intake were not detected by diabetes status.

Serum albumin levels were lower in people with versus without diabetes. Reduced serum albumin levels have been shown to indicate malnutrition risk in people on haemodialysis; additionally, they serve as a powerful predictor of mortality risk in this population. It has been proposed that factors causing low albumin levels, rather than hypoalbuminaemia per se, may be associated with high mortality and morbidity in people on haemodialysis. For example, inflammation, infection, advanced age and hospitalizations have all been associated with hypoalbuminemia and are also associated with poor survival. It is noteworthy that age and C-reactive protein did not differ by diabetes status in the present study.

Regardless of diabetes status, only a minority of people met ISRNM guidelines for energy, protein, sodium or phosphorus. More people with diabetes met the ISRNM guidelines for sodium intake (80–100 mmol/day) and 25% more people with diabetes and elevated malnutrition risk met the ISRNM guidelines for protein intake (1.2–1.4 g/kg/day). A greater percentage of people with elevated malnutrition risk met ISRNM nutrition guidelines regardless of diabetes status. This is likely a function of the cross-sectional study design, such that people at increased risk had been prescribed corrective dietary interventions prior to study onset.

Although infrequently ordered, oral nutrition supplements were prescribed to people with diabetes almost three times more often than to people without diabetes. This is consistent with the greater percentage of people with elevated malnutrition risk among people with diabetes. In-dialysis centre meals

### Table 3

| Nutrient (Intake per day) | Recommended Intake Level | Elevated nutrition risk | Minimal nutrition risk | Diabetes N = 126 | No Diabetes N = 249 | p-value between people with vs. without diabetes |
|---------------------------|--------------------------|-------------------------|------------------------|-----------------|---------------------|-----------------------------------------------|
|                           |                          | N = 74                  | N = 98                 | N = 52          | N = 151             |                                               |
| Energy                    | 30–35 kcal/kg/day        | 24.3%                   | 17.9%                  | 0.04            | 0.08                |                                               |
| Protein                   | 1.2–1.4 g/kg/day         | 40.5%                   | 26.9%                  | 0.04            | 0.08                |                                               |
| Sodium                    | 80–100 mmol/day          | 24.3%                   | 21.2%                  | 0.04            | 0.08                |                                               |
| Phosphorus                | 800–1000 mg/day plus binders if elevated | 24.3% | 15.4% | 0.04 | 0.08 |

All comparisons were made using the chi square test. When a range of intake is presented, the lower cutoff was used to calculate the percentage of subjects meeting the requirement for that nutrient.

### Table 4

| Variable                      | Odds Ratio | 95% Confidence Interval of OR | p-value |
|-------------------------------|------------|-------------------------------|---------|
| Diabetes                      | 2.15       | 1.35–3.43                     | 0.001   |
| C-Reactive Protein (nmol/L)   | 1.02       | 1.00–1.03                     | 0.02    |
| Delivered dialysis dose (Kt/V)| 6.07       | 1.89–9.53                     | 0.002   |
| Haemoglobin (g/L)             | 0.79       | 0.66–0.94                     | 0.008   |
| Age (years)                   | 1.01       | 0.99–1.03                     | 0.16    |
| Men (vs. Women)               | 1.09       | 0.70–1.71                     | 0.69    |
| Years on haemodialysis        | 0.98       | 0.93–1.04                     | 0.52    |

Minimal malnutrition risk was compared to any risk elevation (mild, moderate or severe).

The regression is statistically significant (p < 0.001).
and oral nutrition supplements have been shown to ameliorate deteriorated nutrition status. Oral nutrition supplements tailored for people with kidney disease have been shown to produce lower glucose curves than non-specialized oral nutrition supplements in people with diabetes on haemodialysis.

In the multivariable logistic regression model, diabetes more than doubled the odds of elevated malnutrition risk. Other predictors of this outcome included C-reactive protein, haemoglobin and measured dialysis dose. All of these predictors persisted even after forcing age, sex and years on dialysis into the model.

As with prior reports, the present study indicates that inflammation, represented by C-reactive protein, is associated with elevated malnutrition risk; however, it does not negate the role of diabetes itself, nor does it fully explain the elevated malnutrition risk observed in people with diabetes. Similarly, haemoglobin is known to be inversely associated with malnutrition in people on haemodialysis, consistent with findings in the present study. Again, its presence as a predictor of malnutrition risk did not preclude diabetes as a predictor. In the present study, delivered dialysis dose (Kt/V) was positively associated with elevated malnutrition risk. This positive association has been observed in other cross-sectional studies. Prospective studies, however, report an inverse association between Kt/V and malnutrition. This discrepancy may be reconciled by considering that increasing Kt/V may be a response to identified inflammation and malnutrition; however, temporality is lost in a cross-sectional study design.

Findings of the present study must be considered in the framework of its limitations. First, the present study is cross-sectional, which excludes any discussion of causality. Findings herein demonstrate association only. Second, while the study population was a representative sample of people treated at hospital haemodialysis centres, it did not include individuals treated at community haemodialysis centres, who tend to be younger and have fewer comorbidities. The impact of this might be to over-estimate the prevalence of elevated malnutrition risk in the total haemodialysis population, as per Berkson’s bias. However, even if overestimation of prevalence has occurred, it does not negate or explain elevated malnutrition risk despite greater BMI among people on haemodialysis with diabetes versus without diabetes.

Findings of the present study suggest that people on haemodialysis with diabetes, a group with increased prevalence of overweight and obesity, are nevertheless at increased risk for malnutrition. Both increased total body fat and muscle mass have been shown to be improve survival among people on haemodialysis, a finding consistent across various dialysis-treated populations. Nutrition status should be isolated in future studies of the association between body size and survival in people on haemodialysis.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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