Variable Selection for Assessing Risk Factors for Weight and Body Fat Gain During the First Year After Kidney Transplantation

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Abstract

Background: Body fat and overall weight gain are common after kidney transplantation and are associated with poor clinical outcomes. Therefore, identification of at-risk patients is relevant for preventive interventions. Clinical Question: What variables influence weight and fat gain in patients in the first year after kidney transplantation? Literature Search: Prospective and retrospective cohort studies published in or after 2001 naming fat and/or overall weight gain during the first year after kidney transplantation as outcome variable(s) were systematically searched in Medline/Pubmed in November 2018 and March 2022. Clinical Appraisal: We identified 16 studies examining a wide variety of potential factors influencing weight and fat gain over the first posttransplant years. These included genetic, socio-demographic, behavioral, biomedical, psychological and environmental factors. For a number of variables, study results were contradictory: some studies indicated preventive impacts on weight or fat gain; others concluded that the same factors increased it. Cases were discussed with 2 clinical experts. We eventually agreed on 13 potentially relevant risk factors for post-transplant weight/fat gain: age, gender, genes, income, ethnicity, education, eating habits, physical activity, smoking cessation, baseline BMI, baseline fat, depression and perceived overall wellbeing. Integration into Practice: Before integration into clinical practice, a critical evaluation of all potential risk factors’ suitability for assessment will be necessary. Evaluation: To reduce the list of risk factors to the most relevant, a first testing within a prospectively collected data set is planned.

Keywords: evidence-based practice, body weight changes, kidney transplantation, behavior

Background / Significance of the Problem

Body fat and overall weight gain are common after kidney transplantation, and are known risk factors for poor clinical outcomes such as mortality.1 Even in patients with normal pre-transplant weight, unmonitored weight gain can lead to overweight or obesity.2 Therefore, early identification of patients with a high risk for post-transplantation weight or body fat gain is important, as it allows timely initiation of preventive interventions. To identify risk factors for weight/fat gain in the first year after kidney transplantation, an evidence-based approach was chosen.

Clinical Question

Our clinical question was “What variables influence body fat and overall weight gain during the first year after transplantation?” To ensure that causality could be inferred, only longitudinal studies were included.

Search of the Literature

Medline / Pubmed were searched in November 2018 that included longitudinal prospective and retrospective cohort studies that investigated risk factors for weight gain, body fat gain, or body mass index (BMI) outcomes. Our initial returns were updated in March 2022 using the following search strategy:

1. MeSH DESCRIPTOR Risk Factors
2. MeSH DESCRIPTOR Kidney Transplantation
3. MeSH DESCRIPTORs Body Mass Index OR Obesity OR Overweight OR Obesity, Morbid OR Weight Reduction Programs OR Ideal Body Weight OR Weight Loss OR Weight Gain OR Body Weight Changes OR Body Weight Maintenance OR Resistance Training OR Waist-Height Ratio OR Body WeightAnorexia OR Anorexia Nervosa
4. Underweight
5. 3 OR 4
6. 1 AND 2 AND 5

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Table 1. Risk Factors for Increased Weight (Kg), BMI or Body Fat Percentage at 1-Year Posttransplant.

| Category               | Topic                  | Literature review                                                                 | Expert opinion assessment                      |
|------------------------|------------------------|-----------------------------------------------------------------------------------|------------------------------------------------|
| **Genetic factors**    | Genes                  | Identified as risk factor⁴                                                        | Risk factor                                     |
|                        | Age                    | Controversy: Younger age as risk factor,⁴-⁸ no effect⁹-¹¹                          | An important moderating factor                  |
|                        | Ethnicity              | Controversy: Black ethnicity (vs all other ethnicities) as risk factor for weight gain,⁵-⁷ no effect of black ethnicity (vs all others) on weight gain⁶ ¹² | Risk factor                                     |
|                        | Income                 | Controversy: Lower income as a risk factor for weight gain,⁷ higher income as risk factor for weight gain⁶ | Risk factor in general population               |
|                        | Gender                 | Controversy: Female gender as risk factor for weight gain at month ¹²,⁵, ⁷, ⁸ no effect of gender (either female or male) on weight gain⁶ ⁹ ¹² | Risk factor in general population               |
|                        | Education              | No evidence in kidney transplantation                                              | Risk factor in general population               |
| **Socio-demographic factors** | Age              | Controversy: Younger age as risk factor,⁴-⁸ no effect⁹-¹¹                          | An important moderating factor                  |
|                        | Income                 | Controversy: Lower income as a risk factor for weight gain,⁷ higher income as risk factor for weight gain⁶ | Risk factor in general population               |
|                        | Gender                 | Controversy: Female gender as risk factor for weight gain at month ¹²,⁵, ⁷, ⁸ no effect of gender (either female or male) on weight gain⁶ ⁹ ¹² | Risk factor in general population               |
|                        | Education              | No evidence in kidney transplantation                                              | Risk factor in general population               |
|                        | Smoking cessation      | Lack of evidence in kidney transplantation                                         | Risk factor in general population, eg, Hu 2018¹³ |
| **Behavioural factors** | Eating habit           | Controversy: Self-reported carbohydrate consumption was a risk factor for weight gain in the multivariate model,⁶ other indicators such as baseline kilocalories of energy, total fat, total carbohydrates and total protein on weight gain were identified as risk factors only in simple correlation.⁶ Self-reported percentage of fat intake, percentage carbohydrate, percentage protein intake was not identified as risk factor in either simple or multivariate analyses.⁶ Self-reported intake of mono- & disaccharides, intake of energy-rich drinks/dairy, and vegetable intake were identified as risk factors for fat gain only in mean difference analysis.⁵ Eating habits are known to be the main factor for weight gain, but the applied self-report methods in those studies may not be specific enough. | Risk factor                                      |
|                        | Physical activity      | Identified as risk factor: Lower number of steps per day (assessed with pedometer) and lower self-reported physical activity (time × intensity) as risk factors for fat gain.⁵ Lower number of minutes of moderate-to-vigorous intense activity or more time spent sedentary (assessed with pedometer) were not significantly associated with fat gain. Self-reported physical activity, days of activity and time sleeping were not identified as risk factors for weight gain in a simple correlational design.⁶ | Risk factors in general population               |
|                        | Smoking cessation      | Lack of evidence in kidney transplantation                                         | Risk factor in general population               |
| **Biomedical factors**  | Creatinine during first year / creatinine clearance | Not identified as risk factor: Creatinine clearance during year 1 was not identified as risk factor.¹¹ Lack of evidence: Other studies investigated creatinine only at month ¹²,⁵, ¹⁰ | No risk factor                                   |
|                        | Rejection episodes     | Controversy: Only one study reported having “no rejection episode” as a risk factor for weight gain,⁷ whereas others did not detect a significant association⁵, ¹⁰, ¹¹ | No risk factor, having no rejection may be linked to higher wellbeing |
|                        | Hospitalization episodes | Weak: Lower number of hospitalizations is a risk factor for weight gain⁵          | No risk factor                                   |
|                        | Baseline BMI (at day of transplant) | Identified as risk factor: Higher BMI¹⁵ or obesity (BMI > 30)¹⁴ as risk factor; lower BMI⁶ ¹⁰ or BMI below 25¹⁴ as risk factor | Risk factor                                     |
|                        | Prednisone dose        | Controversy: Cumulative dose¹⁴, ¹⁵ or withdrawal after 100 days¹⁶ were not identified as risk factors in some studies, whereas cumulative dose¹⁰ and steroid withdrawal after 7 days¹⁴, ¹⁷ were identified as risk factor in other studies. | No risk factor                                   |
|                        | CyA/Tac                | Controversy: Type of immunosuppressive medication has effect on weight gain,¹⁰ whereas others do not⁵ | No risk factor                                   |
|                        | Oxidative stress       | Weak: Identified as risk factor in one study (only two group comparison, not regression model)¹⁰ | No risk factor                                   |
|                        | Dyslipidemia           | Controversy: effect of total cholesterol, whereas other parameters (eg High density lipoprotein) were not⁶ ¹⁰ | No risk factor; but associated with metabolic syndrome |
|                        | Higher trunk fat       | Weak: Identified as risk factor⁶                                                  | No risk factor                                   |

(continued)
The literature search yielded 533 articles, the reference lists of which led to 5 more, resulting in a total of 538 articles. Studies were excluded if any of the following criteria applied: No prospective or retrospective cohort design with body weight as outcome (N = 500); review or protocol for future study (N = 4); reporting inconsistencies (N = 1); no measurement at month twelve (N = 10); influencing variables not measured before month twelve (N = 3); not restricted to kidney transplantation (N = 1); or the operationalization of the outcome variable(s) does not allow the drawing of inferences regarding the influencing variable (N = 2); language of publication neither English nor German (N = 1).

### Clinical Appraisal

#### Results of the Literature Review

Of the 538 studies returned by the search, 16 fulfilled the criteria for inclusion in the narrative review. Of those, only 1 focused on body fat gain; the other 15 explored risk factors for weight gain. All included studies were published between 2001 and 2020; the majority (N = 11) were conducted in the United States. Their common strength was their prospective (N = 11) or retrospective (N = 5) cohort design, which clarified the causality both of factors and of outcomes. Their most common limitation was a small sample size: 7 worked with fewer than 100 transplant recipients.

The selected studies investigated a wide variety of risk factors on weight gain over the first years posttransplant. These included genetic, socio-demographic, behavioral, biomedical, psychological and environmental variables. The study results were synthesized narratively. Based on the evidence presented, the risk factors were divided into 5 groups:

- **Identified risk factors**: Genes, lower levels of physical activity, living donation and baseline BMI.
- **Not identified as risk factors**: Creatinine clearance, pre-transplant diabetes, dialysis modality, the presence of calcineurin inhibitors, and haemoglobin levels.
- **Risk factors with controversial results, ie, variables for which some studies reported effects, while others did not or even noted contrary effects**: age, ethnicity, income, gender, eating habits, rejection episodes, prednisone dose, immunosuppressive regimen, dyslipidemia, hypertension, food availability, depression.
- **Risk factors with very weak evidence, ie, those for which only one study found an effect**: number of hospitalization episodes, perceived overall well-being, oxidative stress, and trunk fat.
- **Risk factors with no evidence in kidney transplantation**: For education, smoking cessation and creatinine before month 12, no evidence exists regarding kidney graft recipients.

#### Expert opinions

All factors, but especially those with controversial or weak evidence, were discussed with 2 clinical experts independently. Both experts had broad clinical and research expertise in weight gain and solid organ transplantation, held university degrees (PhD or MD) and had published in this field of research. Any variables that at least 1 expert associated with...
increased risk were counted as potential risk factors. Of the risk factors identified in the literature or those not previously identified as risk factors, the experts assessed only living donation differently from the published evidence: both saw a living donation as associated with better well-being; therefore, the experts recommended not to treat it as a risk factor.

The results of the literature review and expert opinion are displayed in Table 1. Age, gender, genes, income, ethnicity, education, eating habits, physical activity, smoking cessation, baseline BMI, baseline body fat, depression and well-being were identified as potentially relevant factors for posttransplant weight and/or body fat gain.

**Integration into Practice**

Based on the literature review and expert opinions, a number of potential risk factors have been identified. Before these can be integrated into clinical practice, further steps are necessary. One of these is to critically appraise each identified factor’s suitability for clinical use. To do that, the affordability, practicability, effectiveness and cost-effectiveness, acceptability, side-effects and safety, and equity criteria (APEASE) can provide a valuable framework. While age, gender, ethnicity, education, smoking status and BMI fulfill all APEASE criteria and may be ready for adoption into clinical practice, others do not. As a result, those gauged less suitable will be more challenging to integrate into clinical settings.

For example, while assessments of depression and well-being were administered as part of each prospective kidney recipient’s assessment for registration to a graft waiting list, they may not be part of routine follow-up care. Implementing them would be resource-intensive, particularly if administered directly by a psychologist, and may not be well-received by all patients. And while the affordability, practicability, cost-effectiveness and acceptability may all be higher for a different type of operationalization and/or of measurement method, eg, self-reporting via questionnaire, those methods would also likely be less accurate. Consequently, in addition to the APEASE-criteria, each proposed assessment method’s sensitivity and specificity must also be considered.

Similarly, while dual-energy x-ray (DEXA) scans are the gold standard method to measure body fat, their cost per use (including technician time) makes them unrealistic for frequent application. For routine clinical use or home monitoring, various simple, cost-effective and reasonably accurate methods of calculating body composition are available. Bioelectrical impedance analysis (BIA), for example, is very quick, inexpensive and acceptably precise, generally making it a more feasible option.

**Evaluation of Evidence-Based Practice**

To foster the uptake of routine assessment of risk factors for post-transplant weight and body fat gain in post-transplant care, changes in clinical practice should be tailored to the local setting. A careful analysis of that context (ie, values and beliefs, treatment guidelines, reimbursement policies) may help the interventionists engage stakeholders and decision makers from a very early stage. The assessment of body trunk fat, physical activity, depression and well-being, and eating habits requires patient participation and may even involve considerable effort on their part; therefore, acceptance and engagement are keys to enhancing their adoption of this intervention. As implementation outcomes, patients’ and health professionals’ acceptance and adoption of the risk assessment may also function as quality indicators for the evaluation of evidence-based practice.

**Future Areas for Investigation**

The aim of the literature review and expert opinion was to produce a selection of potential factors behind increases in overall weight (BMI) or body fat in the first year following kidney transplantation. It is not yet clear whether these identified have the strongest potential to predict weight gain. Therefore, the next major step will be to reduce the potential risk factors to the most relevant.

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