Effect of high doses of glucocorticoids on cognitive functioning in patients with glomerulopathies

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Introduction

The term *glomerulopathies* or *glomerular diseases (GD)* encompasses numerous renal disorders, usually classified on the basis of the different histopathological patterns of injury. GD lead to progressive glomerular and tubulointerstitial damage, resulting in chronic kidney disease (CKD) development and progression and they constitute up to 20% of end-stage kidney disease (ESKD) cases in Europe.

General management of GD includes the use of nephroprotective medications, such as renin-angiotensin-aldosterone system inhibitors (RAAS-i) and sodium-glucose cotransporter 2 inhibitors (SGLT2-i). However, with an autoimmune process often being involved in the pathogenesis of GD, the treatment may often require administration of immunosuppressive agents, including but not limited to glucocorticosteroids (GCS), rituximab and cyclophosphamide (Figure 1).

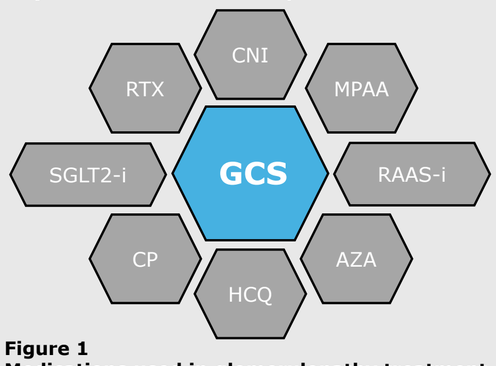


Figure 1
Medications used in glomerulopathy treatment
GCS glucocorticoids ; RTX rituximab ; CNI calcineurin inhibitors ; MPAA mycophenolic acid analogues ; SGLT2-i sodium-glucose cotransporter 2 inhibitors ; RAAS-i renin-angiotensin-aldosterone system inhibitors ; CP cyclophosphamide ; HCQ hydroxychloroquine ; AZA azathioprine

The immunosuppressive treatment regimen is chosen mainly on the bases of symptoms severity and histopathological type of GD, with GCS being often the core of the treatment.

In order to achieve remission, a number of patients with GD require induction therapy with high doses of GCS, followed by slow tapering of the dosage. Afterwards, some of them need prolonged administration of small doses as a maintenance therapy.

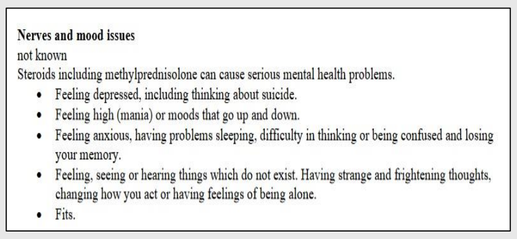

Nerves and mood issues
not known
Steroids including methylprednisolone can cause serious mental health problems.
- Feeling depressed, including thinking about suicide.
- Feeling high (mania) or moods that go up and down.
- Feeling anxious, having problems sleeping, difficulty in thinking or being confused and losing your memory.
- Feeling, seeing or hearing things which do not exist. Having strange and frightening thoughts, changing how you act or having feelings of being alone.
- Fits.

Figure 2
Methylprednisolone patient information leaflet, Pfizer®

GCS have been widely recognized for their numerous side effects, including psychiatric and neurologic (Figure 2). However, the data on their possible detrimental effect on cognitive status are scarce. According to some studies, GCS may have a negative effect on executive functions, recent memory and long-term memory. Noteworthy, none of the studies included patients with renal disorders.

Cognitive tests - novel approach

Aside from neuropsychological tests, novel serum biomarkers are discussed to become supportive in cognitive assessment

Neurofilament light chain (Nf-L)	Brain-derived neurotrophic factor (BDNF)
Biomarker of neuroaxonal injury	Biomarker of memory impairment
Higher serum levels in neurodegeneration process	Higher serum levels correlate with better performance in memory tasks
'The neurologists' troponin'	'A key molecule for memory'

Objectives

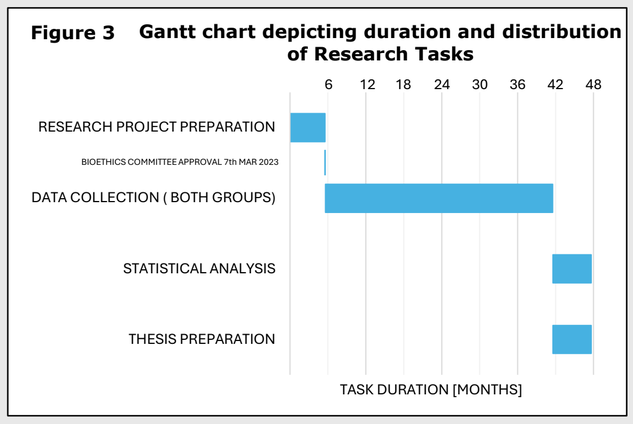
The principal aim of this study is to evaluate the potential effect that high doses of GCS might have on cognitive functioning and Nf-L and BDNF serum levels in patients with glomerulopathies.

Fully understanding the possible impact that GCS might have on cognitive functioning could better enable clinicians and patients to make informed decisions regarding treatment.

Main hypotheses

- There is a difference in cognitive functioning and serum Nf-L and BDNF levels between patients with glomerulopathies treated with high doses of GCS and the control group
- Treatment with high doses of GCS impair cognitive functioning, increases serum Nf-L levels and decreases serum BDNF levels in patients with glomerulopathies
- These changes are temporary and reversible

Materials and methods



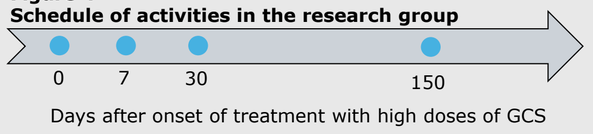
It is an observational, longitudinal, single-center study. The study was approved by the Bioethics Committee of the Medical University of Lodz on 7th of March 2023.
Regarding the low prevalence of GD and longitudinal nature of the study, its' estimated duration is 42 months (Figure 3)

An estimated total number of **80 adult patients** with the diagnosis of GD based on clinical findings and renal biopsy are planned to be included in the study, with approximately 40 patients in each group.

The research group will consist of patients with GD qualified for treatment with high doses of GCS

The control group will consist of patients with GD already undergoing treatment with other immunosuppressive agents and/or very low, maintenance doses of GCS and/or nephroprotective medications

Figure 4
Schedule of activities in the research group



Exclusion criterion: Patients with already established significant cognitive functional impairment are not eligible for the study.

Regardless of the group, the patients will undergo the same procedures (Table 1). In the research group however, the measurements will be performed at four timepoints (Figure 4).

Table 1
Procedures performed at visits

Blood serum sample analysis
- Nf-L (Neurofilament light chain)
- BDNF (Brain-derived neurotrophic factor)
- Creatinine

Spot urine sample analysis
- ACR (albumin to creatinine ratio)

Cognitive tests:
- ACE III (Addenbrook Cognitive Examination)
- FAB (Frontal Assessment Battery)

- Blood and urine samples will be centrifuged, and the supernatant will be frozen at -80°C until further tests.
- **Addenbrook Cognitive Examination** evaluates five cognitive domains: attention, memory, fluency, language and visuospatial processing.
- **Frontal Assessment Battery** is a short screening test to evaluate executive functions.

Results and conclusions

According to our research plan, we are currently in the process of collecting the data needed for further analysis, as depicted in Gantt chart (Figure 3). By the end of April 2024, a total number of 31 participants have been included in the study, 19 in the research group and 12 in the control group (Figure 5, Figure 6). Out of the 19 patients form the research group, 10 of them have already finished the last follow-up. We retrospectively analyzed the demographical and clinical features of patients from both groups (Table 2).

Table 2 Patients' characteristics	Research group		Control group	
Sample size, n	19		12	
Age, mean (SD)	46	(13.9)	45	(14.8)
Sex, n (%)				
Male	12	(63%)	7	(58%)
Female	7	(37%)	5	(42%)
Education, n (%)				
Primary	4	(21%)	1	(8%)
Vocational	4	(21%)	3	(25%)
Secondary	4	(21%)	3	(25%)
Higher	7	(37%)	5	(42%)
24h urine protein, n (%)				
< 1 g	2	(11%)	1	(8%)
1.0 - 1.99 g	4	(22%)	2	(17%)
≥ 2.0 g	13	(68%)	9	(75%)
CKD stage, n (%) (according to KDIGO)				
G1-G2	8	(42%)	6	(50%)
G3	4	(21%)	4	(33%)
G4	5	(26%)	2	(17%)
G5	2	(11%)	0	(0%)

CKD – Chronic Kidney Disease
KDIGO - Kidney Disease Improving Global Outcomes

Figure 5. Graphic depiction of data collection progress in the research group

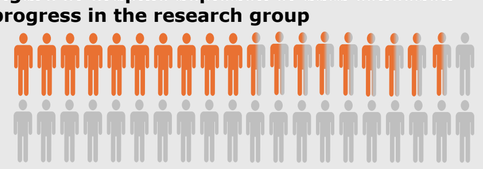


Figure 6. Graphic depiction of data collection progress in the control group

At this point it is too early to draw any conclusions since the groups are still relatively small. However, the pace in which we are gathering the data meets, or even slightly exceeds, the assumptions in the research plan.