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Diseases

Cancer, Ophthalmology & Pediatric

Human Infection Studies

Patients with Diabetic Ketoacidosis

Highlights

Pediatric Emergency Service

Unilateral Idiopathic Neuroretinitis

Discovering Thoughts, Inventing Future

VOLUME 23 ISSUE 3 VERSION 1.0

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Study of Patients with Diabetic Ketoacidosis Admitted at the Pediatric Emergency Service at Children's Hospital Dr. Jeser Amarante Faria

By Patricia Gomes, Lucas Horochoski, Eduardo Procópio Burian de Castro, João Alberto Mucciolo Silva & Suely Keiko Kohara

University of Joinville Region

Abstract- A retrospective study based on the review of medical records in the Tasy system of patients admitted with diabetic ketoacidosis in the emergency service at Children's Hospital Dr. Jeser Amarante Faria, Joinville-SC. 88 medical records were analyzed, corresponding to 71 patients, nine patients with more than one hospitalization, a majority of females (78%), age range from 1.3 to 17.1 years. A mean of five days of hospitalization, with 21 cases requiring hospitalization in the intensive care unit was noted, along with severe diabetic ketoacidosis in 59 consultations. Patients who never had a diabetic decompensation were 44% of the consultations. Hypoglycemia was the most common complication (24%), and no deaths were recorded during the evaluated period. Girls with a mean age of 10 years were the main group admitted with diabetic ketoacidosis, and this medical emergency is still often the first manifestation of type 1 diabetes mellitus in our midst.

Keywords: *diabetes mellitus type1 · diabetic ketoacidosis · pediatrics.*

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Study of Patients with Diabetic Ketoacidosis Admitted at the Pediatric Emergency Service at Children's Hospital Dr. Jeser Amarante Faria

Patricia Gomes [α], Lucas Horochoski [σ], Eduardo Procópio Burian de Castro [ρ], João Alberto Mucciolo Silva [ω] & Suely Keiko Kohara [¥]

Abstract- A retrospective study based on the review of medical records in the Tasy system of patients admitted with diabetic ketoacidosis in the emergency service at Children's Hospital Dr. Jeser Amarante Faria, Joinville-SC. 88 medical records were analyzed, corresponding to 71 patients, nine patients with more than one hospitalization, a majority of females (78%), age range from 1.3 to 17.1 years. A mean of five days of hospitalization, with 21 cases requiring hospitalization in the intensive care unit was noted, along with severe diabetic ketoacidosis in 59 consultations. Patients who never had a diabetic decompensation were 44% of the consultations. Hypoglycemia was the most common complication (24%), and no deaths were recorded during the evaluated period. Girls with a mean age of 10 years were the main group admitted with diabetic ketoacidosis, and this medical emergency is still often the first manifestation of type 1 diabetes mellitus in our midst.

Keywords: diabetes mellitus type1 · diabetic ketoacidosis · pediatrics.

I. Introduction

Diabetes Mellitus (DM) is a metabolic syndrome characterized by the presence of hyperglycemia, and has many possible etiologies. In pediatrics, type 1 diabetes (T1D) is the most prevalent strain of DM, and it is one of the most common childhood chronic diseases.[1]

T1D has an autoimmune etiology, with increasing destruction of pancreatic beta cells, the insulin producers, which leads to their total eradication, and complete exogenous insulin dependency.[2] 90% of cases diagnosed in pediatrics are T1D[3], and approximately 96.100 children under 15 years old develop T1D every year, with an estimate of 586.000 children and teenagers being disease carriers all around the world. Brazil holds the third position of most cases of T1D in persons under 20 years.[4]

Typical T1D symptoms are polyuria, polydipsia, polyphagia and weight loss. When all symptoms are present, a clinical diagnosis is not hard to accomplish. However, with a late diagnosis, the patient can develop Diabetic Ketoacidosis (DK), which has high morbidity and mortality. National data shows a prevalence of 42,3% of T1D patients who were first diagnosed during an episode of DK, but the data have great regional variation.[5]

The DK is a group of many clinical and laboratorial changes caused by insufficient insulin activity and increased counter-regulatory hormone production that begins as an answer to stress situations which alter carbohydrate, fat, and protein metabolism. Glycogenolysis and gluconeogenesis occur to increase glucose production, proteolysis and lipolysis occur to provide substrates to the gluconeogenesis, which results in a ketone bodies production secondary to lipolysis. A cellular catabolism state surges after these metabolic alterations. Osmotic diuresis is a result of sugar in the urine and ketonuria, and leads to metabolic depletion of sodium, potassium and phosphorus, among other minerals.[1,2,4] Vomiting, a result of ketonemia, added to osmotic diuresis causes severe dehydration, and the hypoperfusion state in tissues all over the body aggravates the acidosis by producing lactic acid and reducing the glomerular filtration rate. Increased glucose, ketones and urea levels lead to a hyperosmolar state that induces idiogenic osmoles production by the central nervous system cells.[2]

The main clinical findings in a patient during a DK state are: dehydration, ketonic breath, abdominal pain, vomiting, tachycardia, Kussmaul breathing, low blood perfusion signs, and central nervous system changes may be present.[5] Laboratory findings include hyperglycemia (>200mg/dL), metabolic acidosis (pH<7,3 or HCO_3<15mEq/L), ketonemia and ketonuria, and anion gap elevation.[1]

DK can be divided according to the level of acidosis. Mild DK when pH is 7,3-7,2 or HCO_3 is between 10-15 mEq/L; moderate DK if 7,2-7,1 or HCO_3 is between 5-10mEq/L and severe DK when pH<7,1 or HCO_3<5 mEq/L.[2] Complications such as cerebral edema, acidosis and other major hydroelectrolytic disorders secondary to DK are the main cause of death in children and teenagers with DM.[4]

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Treatment consists in progressive correction of the hydroelectrolytic disorders: a slow and steady reduction of sugar levels in blood along with ketogenesis can be managed with insulin doses administered after the initial expansion phase.

This study aims to demonstrate the characteristics of the patients who were admitted at the emergency room while in DK, how they were managed and the cases outcomes.

II. Methods

Retrospective study with data obtained by reviewing the emergency room archives at the Children's Hospital Dr. Jeser Amarante Faria, Joinville-SC. There were included patients admitted at the Emergency room in the period between january 2013 and december 2017 who were clinically diagnosed with DK and had the following laboratorial findings: hyperglycemia (>200mg/dL), metabolic acidosis (pH<7,3 or HCO_3<15mEq/L), ketonemia or ketonuria. The International Classification of Diseases used to filter out the charts found in the medical records on the PHILIPS Tasy system (Philips Healthcare, Cambridge, MA, USA) were E10.1, E13.1, E14.1 and E10.0. Incomplete or lost charts were excluded from the study. Starting from the data bank built as a Microsoft Excel 2013 sheet, the data was analyzed and presented as statistics. This research was approved by the Hospital Hans Dieter Schmidt/SES/SC ethics and research committee, under the authorization number 3.098.043.

III. Results

There were 97 hospitalizations of 88 patients with DK. Nine patients were hospitalized more than once (one patient arrived seven times at the hospital, another one five times, another one was four times, and six patients were hospitalized two times each, in a time span of five years), totalling 28 admissions. Of these 88 patients, 68% were girls (60). Age range varied from 1.3 to 17.1 years, and 10.7 years were the average age (Table 1).

DK as a T1D first manifestation corresponded to 48 medical attendances, 49% of the total (*p-value* = 0,920) (Figure 1).

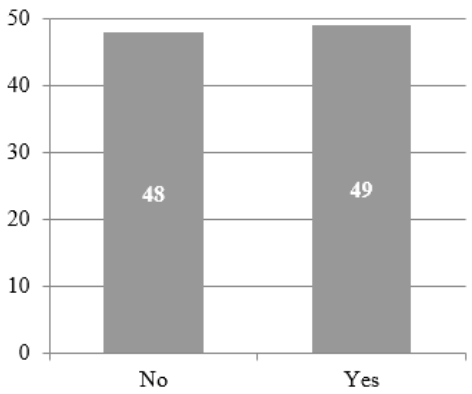

Figure 1: DK as a T1D first manifestation

Severe cases corresponded to 65.9% of the medical attendances, 20.6% were moderate, and 13.4% were the mild cases, considering pH and HCO_3 levels of the arterial gasometry that was first collected.

Among the 97 hospitalizations, 27 were admitted in the Intensive Care Unit (ICU). The patients were, on average, five days in the ICU, but two of them stayed for more than 20 days (one patient during his leukemia treatment and another presented cerebral edema as a complication).

In 28 cases there were complications, hypoglycemia being the most common in 19.5%, hypocalcemia in 9.2%, hypercalcemia in two and hypernatremia in one occasion. Cerebral edema was the most serious complication, happening in one patient but with no deaths.

IV. Discussion

T1D incidence all over the world increased in the last decades, especially among children under 5 years old. An estimate of 30 thousand Brazilians are T1D carriers, and Brazil occupies the third position of countries where T1D has the most prevalence.[4]

It is imperative to recognise the profile of the patients who present DK at the emergency room, as this is the main cause of death among diabetic children and teenagers[2].

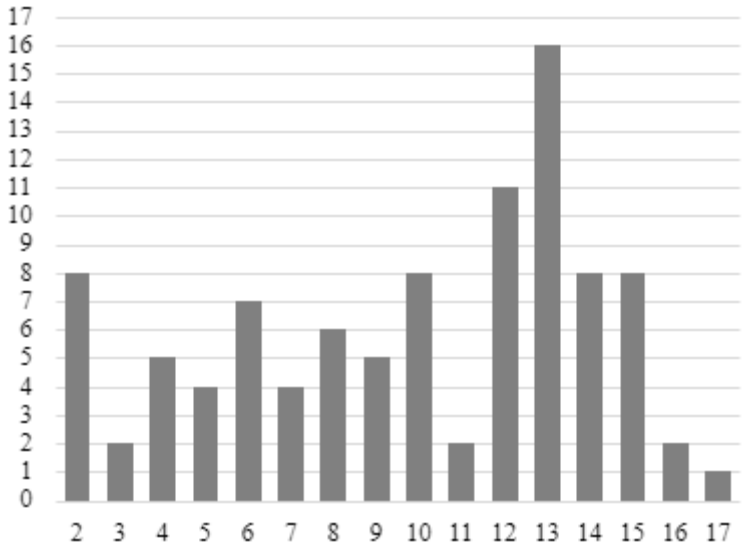

Figure 2: Distribution graphic of number of hospitalization x age in years

By observing the age distribution graphic (Figure 2), it is clear that the teen years are the period in which it is most difficult to accomplish a good metabolic control, therefore the highest incidence of DK complications happen during this period.[6]

In this study, 49.4% (*p-value* = 0,920) of the hospitalizations corresponded to first decompensation situations. In a large national study, the Brazilian T1D Study Group (BrazDiab1SG)[4], 3591 patients with T1D (56% feminine sex) were evaluated at public institutions, and it was found that 42.3% of patients with T1D were diagnosed with the condition during a DK episode, a similar result was obtained in our study, like in other literatures. The glycemic decompensation is usually longer and more severe in newly diagnosed patients with T1D.[6]

Insulin was first used in the 1950s, when the mortality rate was up to 10%. Today, there are specialized centers with focus on the treatment of DK, where the mortality rate in general is below 1%.[4] Fortunately, no deaths were recorded at the analyzed period. Cerebral edema, considered the most feared complication, occurred only once, with a positive outcome.

The analysis of the patients characteristics in this study showed that DK was most frequent in girls at 10 years of age. It still is very common that the first manifestation of T1D is the sudden and serious DK. Although a medical emergency, the appropriate management increases the chances of a positive outcome.

Author´s contribuitions

Study design: Kohara SK

Data collection: Gomes P, Horochoski L, Castro EPB, Silva JAM

Data analysis: Gomes P, Horochoski L, Castro EPB, Silva JAM

Manuscript writing: Gomes P, Horochoski L, Castro EPB, Silva JAM

Manuscript revision: Gomes P, Kohara SK

Study supervision: Kohara SK

Declaration: The data underlying the research text are contained in the manuscript in the form of tables. However, the database contains patient records and personal data, which is why they will be available on demand with the corresponding author.

Conflict of interests

The authors declare that they have no conflict of interest.

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Table 1: Data collection

Hospitalization number	Age (years)	Sex (M/F)	DK as a T1D first manifestation	Severity	Admitted in ICU	Complications
1	6,8	Female	No	Severe	No	No
2	15,8	Male	Yes	Severe	No	No
3	6,8	Male	No	Moderate	No	No
4	14,7	Female	Yes	Moderate	No	No
5	11,5	Female	Yes	Severe	No	No
6	10,5	Female	Yes	Moderate	No	No
7	13,7	Female	Yes	Severe	No	No
8	15,1	Female	Yes	Severe	No	No
9	6,7	Female	No	Severe	No	No
10	12,2	Male	No	Severe	Yes	No
11	13,5	Female	No	Moderate	Yes	No
12	8,1	Male	No	Mild	No	No
13	12,6	Female	Yes	Severe	Yes	No
14	15,1	Male	No	Severe	No	No

Hospitalization number	Age (years)	Sex (M/F)	DK as a T1D first manifestation	Severity	Admitted in ICU	Complications
15	13,5	Male	Yes	Severe	Yes	No
16	7,2	Female	No	Moderate	No	No
17	13,5	Female	Yes	Mild	No	No
18	3,1	Female	Yes	Severe	No	No
19	9,8	Female	No	Mild	No	No
20	7,4	Female	No	Severe	No	No
21	14,6	Male	Yes	Severe	No	No
22	15,9	Male	Yes	Severe	Yes	No
23	14,2	Female	Yes	Mild	No	No
24	15,8	Female	Yes	Severe	No	No
25	1,8	Female	No	Severe	No	No
26	13,4	Female	Yes	Severe	No	No
27	10,4	Female	Yes	Severe	No	Hyperkalemia
28	5,0	Female	Yes	Moderate	No	Hypoglycemia
29	4,1	Female	No	Moderate	No	No
30	10,0	Male	No	Severe	Yes	Hypokalemia
31	10,1	Female	No	Severe	No	No
32	12,6	Female	Yes	Severe	No	Hypoglycemia
33	13,1	Female	Yes	Moderate	No	Hypoglycemia
34	13,3	Female	Yes	Severe	No	No
35	14,1	Female	Yes	Moderate	No	No
36	10,7	Male	No	Severe	Yes	No
37	14,9	Female	Yes	Severe	No	No
38	5,1	Female	Yes	Moderate	No	Hypoglycemia
39	16,8	Female	Yes	Moderate	No	No
40	10,5	Male	No	Severe	No	No

Hospitalization number	Age (years)	Sex (M/F)	DK as a T1D first manifestation	Severity	Admitted in ICU	Complications
41	12,1	Male	Yes	Moderate	No	No
42	4,7	Female	No	Mild	No	Hypoglycemia
43	13,2	Female	No	Mild	No	Hypokalemia
44	13,1	Male	Yes	Severe	No	No
45	4,5	Female	No	Mild	No	No
46	6,1	Female	Yes	Moderate	No	No
47	8,3	Female	Yes	Moderate	No	Hypoglycemia
48	8,9	Female	Yes	Severe	No	No
49	8,9	Female	Yes	Severe	Yes	Hypoglycemia
50	2,1	Male	No	Severe	No	No
51	5,9	Female	Yes	Severe	Yes	Hypoglycemia
52	15,1	Male	Yes	Severe	Yes	No
53	6,9	Female	No	Moderate	No	No
54	2,0	Female	No	Severe	Yes	Hypokalemia
55	15,6	Female	No	Severe	Yes	Cerebral edema
56	11,2	Female	Yes	Moderate	No	No
57	12,3	Female	Yes	Severe	No	Hypoglycemia
58	13,2	Female	Yes	Severe	No	No
59	13,4	Female	Yes	Severe	No	No
60	13,5	Female	Yes	Severe	No	No
61	13,9	Female	Yes	Severe	No	No
62	14,8	Female	Yes	Severe	No	No
63	10,1	Male	Yes	Severe	No	No
64	13,1	Male	Yes	Severe	No	No
65	16,0	Female	Yes	Severe	No	No
66	5,4	Female	Yes	Severe	No	No

Hospitalization number	Age (years)	Sex (M/F)	DK as a T1D first manifestation	Severity	Admitted in ICU	Complications
67	17,1	Male	Yes	Severe	Yes	Hypoglycemia
68	8,4	Male	No	Moderate	No	No
69	6,6	Male	No	Mild	No	Hypoglycemia
70	6,3	Female	No	Severe	Yes	No
71	8,0	Male	No	Moderate	No	No
72	12,4	Female	Yes	Severe	Yes	Hypokalemia
73	12,8	Female	Yes	Severe	Yes	Hypokalemia
74	13,1	Female	No	Severe	Yes	No
75	3,2	Male	No	Mild	No	Hypoglycemia
76	12,7	Male	No	Mild	No	No
77	14,8	Female	No	Severe	Yes	Hypokalemia
78	7,1	Male	Yes	Mild	No	Hypoglycemia
79	7,4	Male	Yes	Severe	No	Hypoglycemia
80	15,0	Male	No	Severe	No	No
81	1,5	Female	No	Mild	Yes	No
82	1,3	Male	No	Severe	No	No
83	14,8	Male	Yes	Severe	Yes	No
84	2,4	Male	No	Mild	No	Hypoglycemia
85	9,1	Male	No	Severe	No	No
86	9,3	Male	No	Severe	Yes	Hypokalemia
87	13,1	Female	No	Severe	No	No
88	12,3	Male	No	Severe	No	No
89	4,5	Male	No	Severe	Yes	Hypokalemia
90	2,5	Male	No	Moderate	Yes	No
91	2,5	Female	No	Severe	Yes	Hypokalemia
92	4,5	Male	No	Severe	Yes	Hypokalemia

Hospitalization number	Age (years)	Sex (M/F)	DK as a T1D first manifestation	Severity	Admitted in ICU	Complications
93	10,3	Female	No	Severe	Yes	No
94	12,8	Male	No	Severe	No	No
95	12,6	Female	No	Severe	Yes	Hypernatremia
96	9,1	Male	No	Moderate	No	No
97	9,5	Female	No	Severe	No	No

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Unilateral Idiopathic Neuroretinitis Following Pfizer-Biontech COVID-19 Vaccine; A Case Report

By Louis Antoine Bonnet, Nishanthan Ramachandran, John Ah-Chan & Thiyaga Krishnan

Abstract- This case report describes a temporal relationship of unilateral neuroretinitis following the second Pfizer-BioNTech COVID-19 (Pfizer) vaccine. A 16-year-old male of mixed ethnicity presented with gradual loss of vision and pain on eye movement in his left eye 12 days after his second Pfizer vaccine. His visual acuity in the left eye was count fingers at half a meter. There was optic nerve head swelling, macular exudates in a star-shaped pattern with peripapillary and foveal subretinal fluid consistent with left neuroretinitis. His serological and radiologic investigations were negative for any alternative aetiology. He was commenced on doxycycline, rifampicin and oral prednisone on a tapering dose. 4 months after presentation his left eye vision improved to 6/24-2; limited by loss to the outer retinal layers over the fovea. The close proximity of the second Pfizer vaccine dose poses a temporal association with plausible causation.

Keywords: neuroretinitis, COVID-19, SARS-CoV-2, Pfizer, New Zealand.

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Unilateral Idiopathic Neuroretinitis Following Pfizer-Biontech COVID-19 Vaccine; A Case Report

Louis Antoine Bonnet [α], Nishanthan Ramachandran [σ], John Ah-Chan [ρ] & Thiyaga Krishnan [ω]

Abstract- **This case report describes a temporal relationship of unilateral neuroretinitis following the second Pfizer-BioNTech COVID-19 (Pfizer) vaccine. A 16-year-old male of mixed ethnicity presented with gradual loss of vision and pain on eye movement in his left eye 12 days after his second Pfizer vaccine. His visual acuity in the left eye was count fingers at half a meter. There was optic nerve head swelling, macular exudates in a star-shaped pattern with peripapillary and foveal subretinal fluid consistent with left neuroretinitis. His serological and radiologic investigations were negative for any alternative aetiology. He was commenced on doxycycline, rifampicin and oral prednisone on a tapering dose. 4 months after presentation his left eye vision improved to 6/24-2; limited by loss to the outer retinal layers over the fovea. The close proximity of the second Pfizer vaccine dose poses a temporal association with plausible causation.**

Keywords: neuroretinitis, COVID-19, SARS-CoV-2, Pfizer, New Zealand.

I. Introduction

Successive vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) formed one of the primary public health strategies during the COVID-19 pandemic. Pfizer- BioNTech COVID-19 (Pfizer), is the nationally approved and disseminated vaccine in New Zealand (NZ).[1] This mRNA vaccine is provided as an intramuscular injection with two sequential doses required at a 3-4 week interval to achieve satisfactory immunogenicity.[2] Due to the relative infancy of Pfizer's commercial use its ocular side effect profile is continuing to emerge, particularly from anecdotal accounts. This case report describes a temporal relationship of unilateral neuroretinitis following the second Pfizer vaccine, providing evidence for a potentially rare vaccine-related side-effect.

II. Case Report

A 16-year-old male of Maori, Pacific Islander and NZ European background, presented to a regional ophthalmology service with a 12-day history of gradual vision loss in his left eye and pain on eye movement. Review of systems was negative, with no constitutional symptoms. He had limited exposure to farm animals with no direct exposure to domestic animals such as cats. He was not sexually active, denied intravenous drug use and had no history of overseas travel. However, he recently had two successive doses of the Pfizer-BioNTech COVID-19, with his second vaccination 24 days prior to presentation and 12 days prior to symptom onset.

On examination, his visual acuity in the right eye was 6/4.5 while his left eye was counting fingers. His intraocular pressures were 16mmHg and 10mmHg in his right and left eye respectively. He had a grade III left relative afferent pupillary defect (RAPD). Whilst he had full range of eye movement, there was pain on moving his left eye. His left optic nerve was grossly swollen with a macular star (figure 1). There was no anterior chamber inflammation or vitritis. Optical coherence of the retinal nerve fibre layer (OCT RNFL) assessment showed an average RNFL thickness of 481µm, with peripapillary subretinal fluid extending to the fovea (figure 2). Automated perimetry demonstrated an early central scotoma in the left visual field with mean deviation (MD) -4.35 dB. He had a normal right ocular examination and ancillary investigations. Clinical examination and investigations were consistent with left neuroretinitis.

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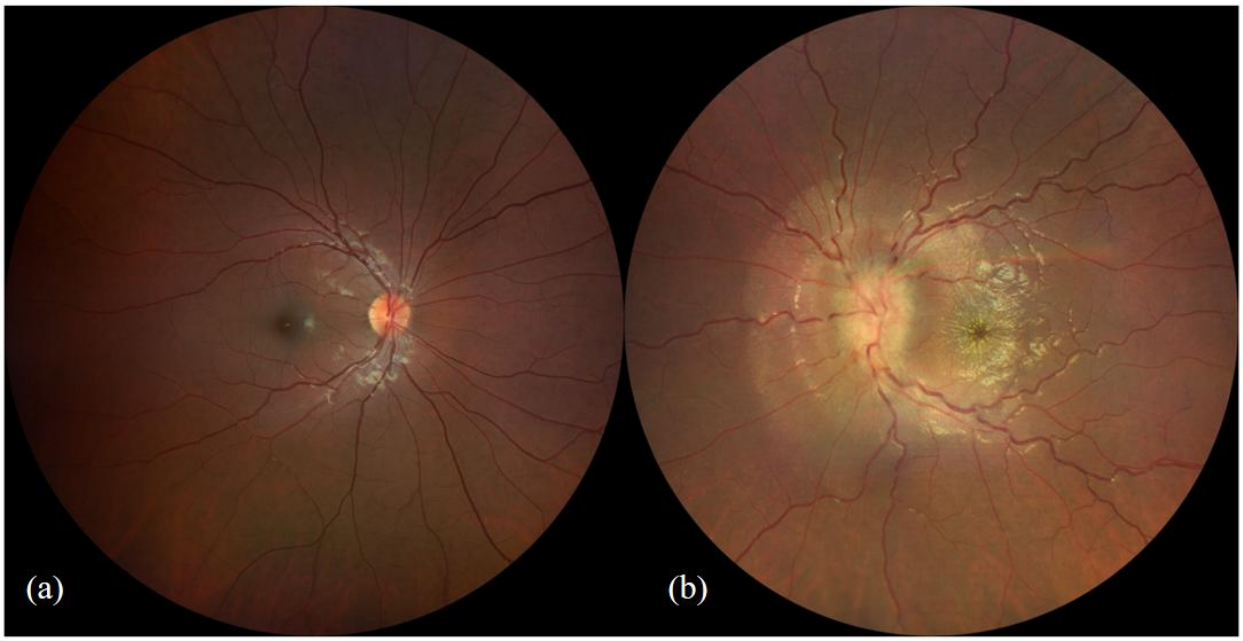

Figure 1: Fundus photography of right eye (a) and left eye (b). The left eye demonstrates diffuse optic nerve head swelling with macular hard-exudates in a star pattern characteristic of left neuroretinitis.

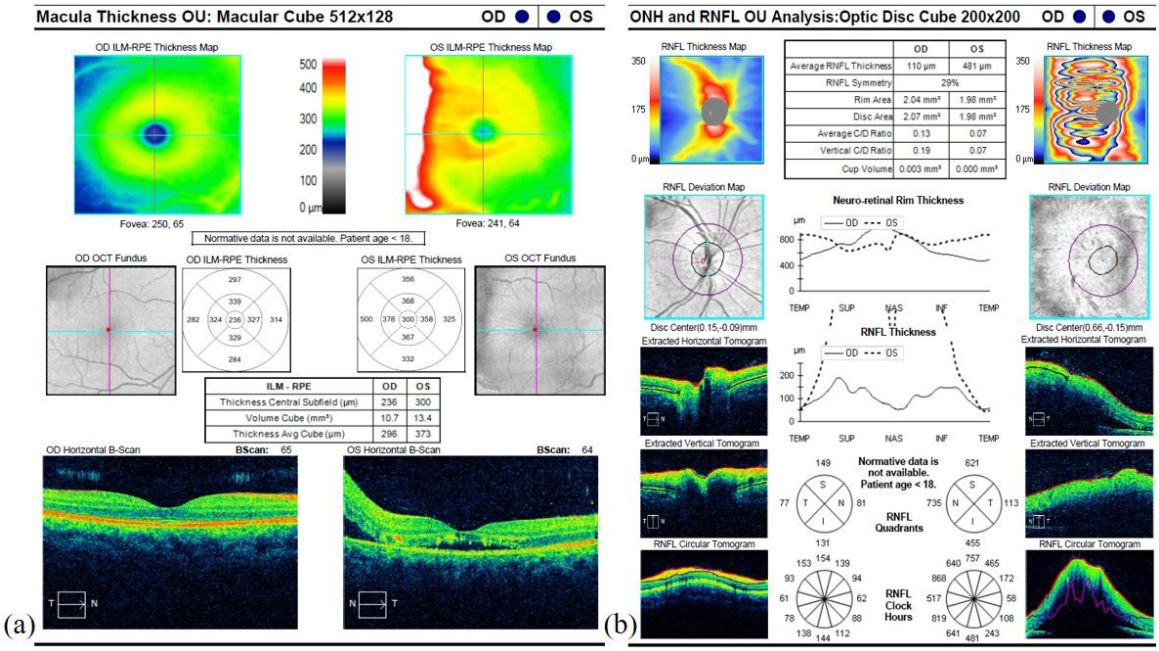

Figure 2: Zeiss OCT macular 512x128 cube (a) and disc RNFL 200x200 cube (b) of both eyes. The left eye demonstrates optic nerve head oedema (b) with peripapillary and foveal subretinal fluid (a).

The patient's infectious screen was negative. This included; Quantiferon-TB Gold, Syphilis, Bartonella henselae immunoglobulin G (IgG)/immunoglobulin M (IgM), human immunodeficiency virus (HIV) antigen and antibody (Ag/Ab), cytomegalovirus (CMV) IgG/IgM, Toxoplasma IgG/IgM and Leptospiral IgM enzyme-linked immunosorbent assay (ELA). Serum angiotensin converting enzyme (ACE) and chest x-ray were normal. Lyme disease serology (Borrelia burgdorferi) was not tested as he had not travelled outside of NZ. Bartonella henselae serology was negative when sequentially tested on initial presentation as well as 4 and 8 weeks later. He had a normal full blood count, liver function, renal function, serum folate and B12. His antinuclear antibodies (ANA) were weakly positive and inconclusive with negative extractable nuclear antigen (ENA), antineutrophil cytoplasmic antibodies (ANCA) and double-stranded deoxyribonucleic acid 40 (dsDNA). Neuromyelitis optica (NMO) IgG antibodies were initially positive however negative on repeat testing 4 weeks

later including negative myelin oligodendrocyte glycoprotein (MOG) antibodies. Magnetic resonance imaging (MRI) of the head, orbits and spine with gadovist contrast were consistent with left retrobulbar optic neuritis without intracranial or spinal involvement (figure 3).

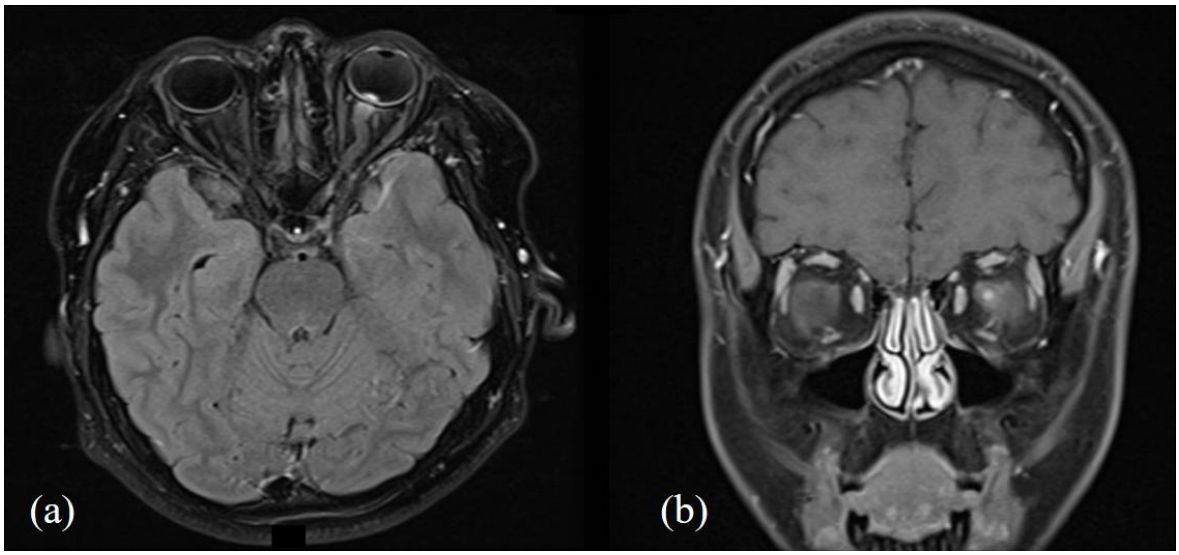

Figure 3: MRI head and orbits with (a); T2 axial TSE FLAIR sequence and (b); T1 coronal TSE Dixon sequence with contrast. Focal enhancement of the anterior margin of the left optic nerve at its junction with the globe is demonstrated without other demyelination or parenchymal intracranial pathology.

The patient was discussed with infectious disease and neurology subspecialties and subsequently commenced on doxycycline 100mg twice a day, rifampicin 300mg twice a day and oral prednisone 60mg daily tapered by 10mg per week over for a total of six weeks. He was also supplemented with Vitamin D3. The patient's retrobulbar pain improved within a week of treatment commencement. His best-corrected vision improved to 6/24-2 four months after presentation. His RAPD resolved completely however due to subfoveal outer retinal disruption he continued to demonstrate reduced vision (figure 4e). The optic nerve head swelling improved with resolution of peripapillary and foveal subretinal fluid. His macular hard exudates, previously in a star-shaped pattern, also improved, as did his early visual field defect on automated perimetry. The patient remains under the care of ophthalmology and neurology outpatient departments with ongoing follow-up at time of publishing.

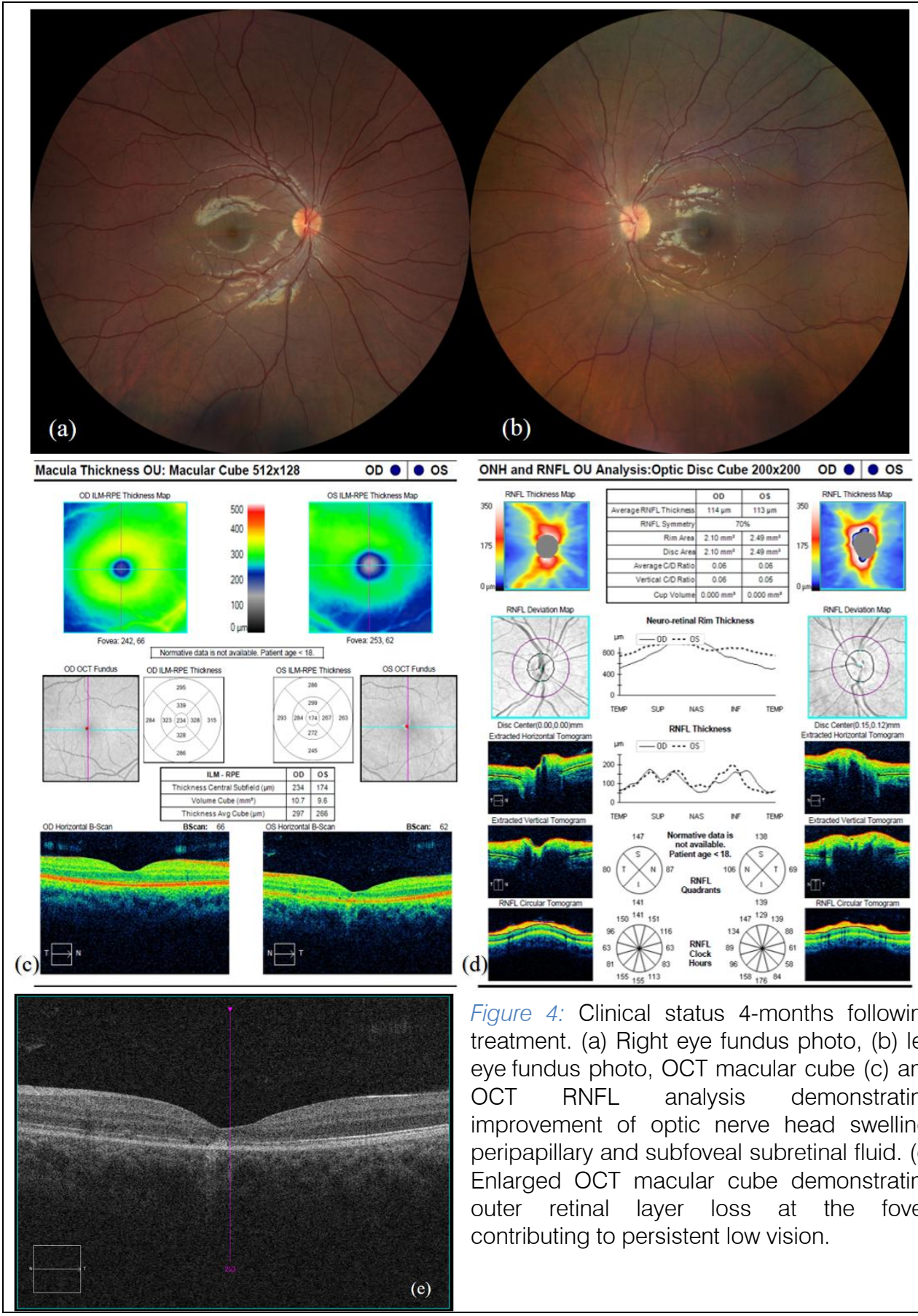

Figure 4: Clinical status 4-months following treatment. (a) Right eye fundus photo, (b) left eye fundus photo, OCT macular cube (c) and OCT RNFL analysis demonstrating improvement of optic nerve head swelling, peripapillary and subfoveal subretinal fluid. (e) Enlarged OCT macular cube demonstrating outer retinal layer loss at the fovea contributing to persistent low vision.

III. Discussion

An increasing number of case reports and retrospective case studies have emerged detailing possible adverse effects of vaccination against COVID-19.[3,4] These appear to encompass a wide variety of ophthalmic manifestations; including orbital, corneal, uveitic, retinal and neurological disorders.[3] Given the strong association between uveitis and immunologic phenomena, a relationship between vaccination and uveitis would be expected.[3] Pavesio et al. identified 70 patients presenting with ocular inflammatory events within 14 days following COVID-19 vaccination with a mean age of 51 years.[4] Elhusseiny et al. reviewed fourteen reports involving 34 patients reporting uveitis after COVID-19 vaccination. The average age at the time of presentation was 47.6 ± 16.3 years, with the average time from vaccination to development of ophthalmic symptoms 8.0 ± 8.6 days.[3]

In a review of adverse ocular events from 2010 to 2020, optic neuritis was found to be the most common event associated with nine different vaccines with a mean onset of 10.8 days post- injection. Five patients receiving COVID-19 vaccination were diagnosed with post-vaccination central nervous system inflammatory syndrome leading to neuroretinitis and papillitis. The mean age at the time of presentation was 48.0 ± 21.5 years, and the average time from vaccination to development of ophthalmic symptoms was 8.6 ± 8.3 days. Three of them presented with bilateral involvement. Significant improvement in symptoms and examination was achieved with use of intravenous methylprednisolone.[3]

Neuroretinitis is a focal inflammatory optic neuropathy characterised by unilateral optic disc oedema and macular exudates.[5] Both infectious and non-infectious aetiologies are recognised with Cat-Scratch Disease (Bartonella henselae) being the most common identifiable cause.[6] The patient presented had serial tests for Bartonella henselae with IgG titres being consistently <64 with negative IgM results. Approximately 25% of neuroretinits cases are considered idiopathic where no definitive cause is determined after thorough investigation.[7] The close proximity of the second Pfizer vaccine dose poses a temporal association with plausible causation. The patient was neither symptomatic nor tested positive to SARS-CoV-2 preceding onset of his ocular symptoms. Lee et al, described a similar case-report of unilateral neuroretinitis of an 83-year old Korean woman following her second dose of the Pfizer vaccine.[8] Visual loss, to the point of hand-movement perception, occurred two days after receiving the second Pfizer vaccine with no background primary ocular history. She was commenced on three days of 1g intravenous methylprednisolone, followed by oral prednisone taper.[8] Although initial visual improvement was witnessed during the first month of treatment, her vison remained finger-counting perception after six months. Lee et al postulated that the low vision was at least partly due to photoreceptor disruption due to persistent subretinal fluid.[8] Likewise, whilst there was considerable improvement to vision and status of the disc and macula in our patient over a four-month period, his visual acuity remained at 6/24-2 secondary to continued sub foveal photoreceptor disruption. Of note, in contrast to the case presented by Lee et al our patient had the typical clinical features of neuroretinitis with the presence of a macular star. Although the demographics and visual outcomes of the two cases may differ, they share an interesting temporal similarity of ocular disease following the second Pfizer vaccine dose. Cheng and Margo et al, suggested that vaccine-related side effects, particularly within close proximity of initial administration may be attributable to an immediate hypersensitivity-type reaction.[9] As the Pfizer vaccine is still relatively novel with respect to its known ocular side-effect profile, this case report poses a temporal relationship with high plausibility. Case reports such as these provide important insight to potential rare-side-effects of a widely disseminated global vaccine.

Disclosure statements

The authors have no conflicts of interest to declare.

Statement of Ethics

Informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Outside the participant's informed consent, ethical approval was not required in accordance with local guidelines and policy.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Human Infection Studies and the SARS-Cov-2 Pandemic

By Jörg Tremmel

Introduction- What could humanity have done better in fighting the SARS-CoV-2 pandemic? From a financial and scientific point of view, it has done many things right, but a crucial ethical question has remained rather unexamined. In this paper, I argue that controlled human infection studies (HIS) would have been ethically justifiable and the right way forward in developing a vaccine against Covid-19. The phase 2/3 trials of the vaccines from AstraZeneca, Pfizer/Biontech and Moderna took between 112 and 196 days. Human challenge trials would have taken much less time, about 30 days. In retrospect, these three vaccines could have been launched 82 to 166 days earlier than they actually were. If this had happened, hundreds of thousands of deaths and millions of hospitalisations worldwide could have been avoided due to the cumulative effect. In terms of preparatory measures for the next pandemic, the ethical discussion on HIS is of utmost relevance for the well-being of future generations.

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Human Infection Studies and the SARS-Cov-2 Pandemic

Jörg Tremmel

Introduction

What could humanity have done better in fighting the SARS-CoV-2 pandemic? From a financial and scientific point of view, it has done many things right, but a crucial ethical question has remained rather unexamined. In this paper, I argue that controlled human infection studies (HIS)[1] would have been ethically justifiable and the right way forward in developing a vaccine against Covid-19. The phase 2/3 trials of the vaccines from AstraZeneca, Pfizer/Biontech and Moderna took between 112 and 196 days. Human challenge trials would have taken much less time, about 30 days. In retrospect, these three vaccines could have been launched 82 to 166 days earlier than they actually were. If this had happened, hundreds of thousands of deaths and millions of hospitalisations worldwide could have been avoided due to the cumulative effect. In terms of preparatory measures for the next pandemic, the ethical discussion on HIS is of utmost relevance for the well-being of future generations.

Phase 1 study: the first use of vaccines on humans

In order to understand the ethical issues surrounding HIS, it is necessary to understand how vaccines are tested on humans. Once vaccine developers have tested a certain agent against an infectious disease in animals ('preclinical studies') and these creatures have been successfully immunised, the next step is the first application in humans. The immune system of humans is so fundamentally different from that of even the animals most similar to us, that the approval of an investigational vaccine solely on the basis of animal experiments is not an option. Depending on the number of test persons and the exact question, a distinction is usually made between three phases (and occasionally a phase 4 after approval) in human application. For human volunteers, phase 1 (first in human), poses the greatest risk.

How would one have proceeded in a human infection study?

Regulatory authorities need data on the efficacy of vaccine candidates beyond the results of the phase 1 trial for their decisions. Let us assume that HIS were ethically permissible. In such a scenario, the process to SARS-CoV-2 vaccine could have consisted as described in chart 1.

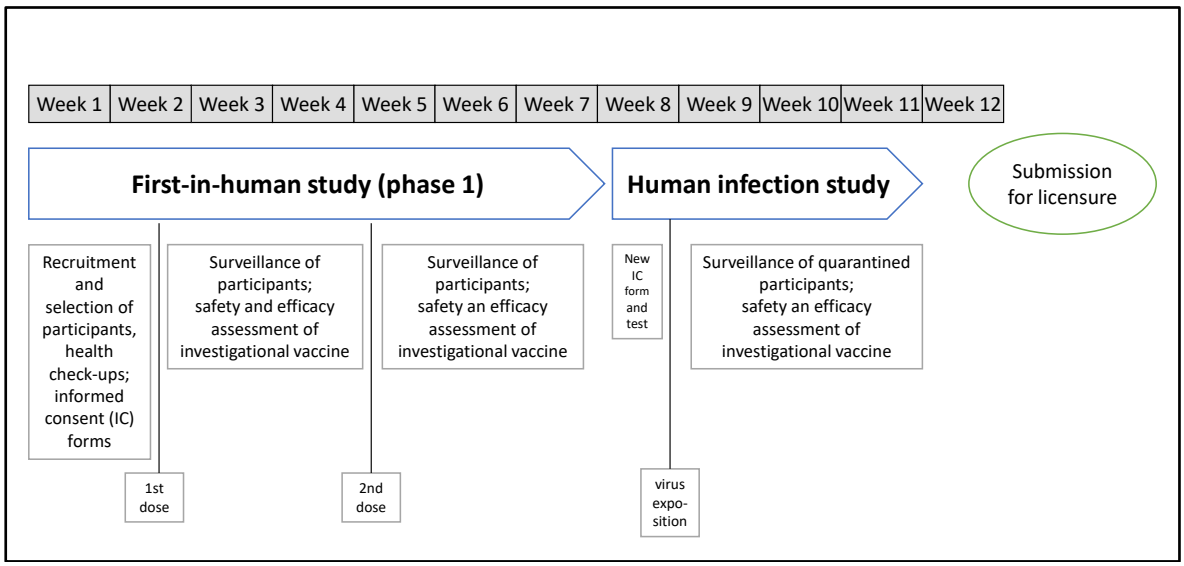

Chart 1: Process to SARS-CoV-2 vaccine licensure, including a phase 1 and a human infection study (hypothetical)

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[1] Synonyms are Human Challenge Studies (HCS) or Human Challenge Trials (HCT).

How approved vaccines against Covid-19 were actually tested in the field?

Time is the decisive factor in protecting future generations from new pandemics.[2] As HIS studies can replace phase 2/3 studies (but not phase 1 studies), it is important to know exactly how long the phase 2/3 studies lasted.[3] The following table shows the relevant data for the first vaccines approved in the EU and the USA, i.e. those from PfizerBiontech, Moderna and AstraZeneca,[4] as well as for the CureVac vaccine CVnCoV.[5]

Table 1: Duration of phase 2/3 studies in the process to SARS-CoV-2 vaccine licensure (de facto)

	Duration of the phase 2/3 study	Participants	Infected persons in the active agent group	Infected persons in the placebo group	Effectiveness of the vaccine
BNT162b2 (Pfizer/ BioNTech)	***115 days*** *27.07.2020 - 18.11.2020*	43.448	8	162	95%
mRNA-1273 (Moderna)	***112 days*** *27.07.2020 - 15.11.2020*	30.420	11	185	94,1%
ChAdOx (AstraZeneca)	***196 days*** *23.04.2020 - 4.11.2020*	23.848	The values of these columns are not comparable, as the phase 3 study was divided into two sub-studies, and the summation of the values was strongly criticised within the scientific community.		
CVnCOV[6] (CureVac)	***123 days*** *11.12.2020 - 12.04.2021*	39.680	83	145	48,2%

The phase 3 trials of the first vaccines approved in the EU and the USA took between 112 (Moderna) and 196 (AstraZeneca) days, depending on the vaccine. Human infection studies would have taken significantly less time, about 30 days. In retrospect, therefore, the vaccines that were gradually approved could have been on the market 82 to 166 days earlier than they actually were. Indeed, a large number of deaths and hospitalisations could have been avoided if HIS had been used instead of the usual phase 2/3 trials.

Without HIS, the following adversities occur. The stronger the protective measures (i.e. lock- down), the more months are lost. The crucial question, how many infected people must there be before the regulatory authorities are satisfied is an opaque process. This is where vaccine manufacturers and regulatory authorities have to come to an agreement. Ultimately, these are negotiation processes that are hidden from the public. Different actors - the government, the regulatory authorities, the public – have different ideas, which can lead to tensions. An example from Turkey: "The Turkish researchers, speaking alongside Health Minister FahrettinKoca, said 26 of the 29 people who were infected during the trial were given placebos, adding the trial would continue until 40 people become infected.

[2] Tremmel 2021.

[3] This refers to the large trial study with thousands of participants. In practice, this is not always referred to as Phase 3, but also as Phase 2/3, Phase 2a/3 or Phase 2b/3, depending on the circumstances.

[4] Johnson & Johnson is not included here because only one dose was administered here. This automatically reduces the time for the clinical trials. As it turned out, however, the immune protection also suffered.

[5] Baden et al 2021; Polack et al 2020; Voysey et al 2021; Kremsner et al 2021b.

[6] It is obvious that CureVac came along later than the competing companies. The Paul Ehrlich Institute had already approved the first 'first in human' study of a vaccine against Covid-19 in Germany on 22 April 2020, namely for four mRNA-based vaccine candidates from the company BioNTech. CureVac ultimately had to refrain from seeking market approval from the regulatory authorities due to the lower efficacy of its vaccine compared to the vaccines approved until the end of 2020.

(...)" Health Minister Koca said Ankara would now – this was on *24 Dec 2020* –approve the vaccine, although "researchers initially planned to announce the results after 40 people were infected." [7] Now, how decides here at what point the vaccine candidate is safe? Incidentally, the vaccine in question was China's Sinovac vaccine, and the vaccine effectiveness of 91.25% calculated on the basis of the small number of cases, which the Turkish health minister communicated to the public, is doubtful. However, this is also true for the decimal places in the vaccine efficacy calculated by e.g. PfizerBiontech or Moderna from the low infection cases of their respective studies. Waiting to see when 10, 20, 30, 40, 60, 80 or 100 vaccinated people will 'accidentally' be infected is gruelling when the whole world is waiting for a vaccine. And the small numbers lead to unsatisfying data about vaccine effectiveness.

Ethical requirements for HIS in general

Uncontrolled pandemics are among the existential risks for future generations. The potential of HIS to reduce this risk is undisputed and this potential was once again highlighted by the WHO in 2020 during the first wave of the Corona pandemic: "Well designed human challenge studies provide one of the most efficient and scientifically powerful means for testing vaccines, especially because animal models are not adequately generalizable to humans. Challenge studies could thus be associated with substantial public health benefit in so far as they (a) accelerate vaccine development, (b) increase the likelihood that the most effective (candidate) vaccines will ultimately become available, (c) validate tests of immunity, and (d) improve knowledge regarding SARS-CoV-2 infection and transmission." [8]

Can the worst effects of pandemics be avoided in *general, i.e. also in the future,* if humanity relies on HIS? That depends on many virological-medical factors. From an ethical point of view, one cannot come to a simple yes or no conclusion in respect to HIS. The following factors and framework conditions play a role in determining the answer:

1. Nature of the pathogen – benefit of a vaccine

HIS have helped in the early research with smallpox, yellow fever and malaria that eventually changed the course of global public health. And HIS have recently helped, for example, to accelerate the development of vaccines against typhoid and cholera.[9] Whether vaccines help in the long term depends also on the ability of a virus to generate immune escape variants. The ability to mutate varies from the genetically stable smallpox virus at one end of the scale to the very rapidly mutating influenza viruses at the other. SARS-CoV-2 is somewhat in the middle.

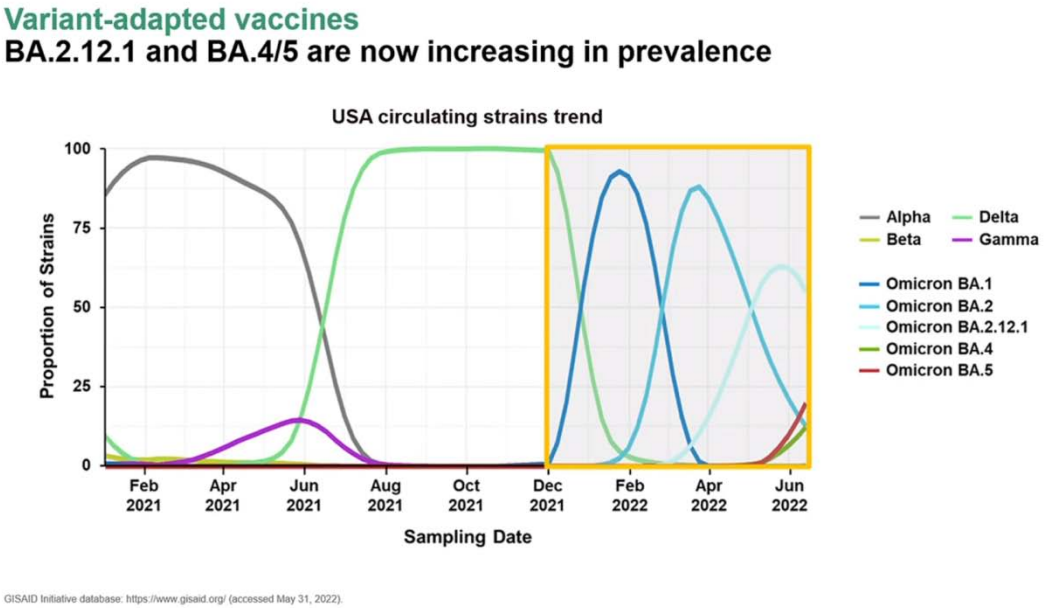

Chart 2: Circulating strain trends in the USA

[7] Gumrukcu/ Kucukgocmen (2020).

[8] WHO 2020: 2.

[9] WHO 2020: 2; Jamrozik/Selegelid 2021.

This means vaccination is a useful but not a perfect remedy. This is the case for most infectious diseases. All experts agree: If mankind had failed to develop vaccines against SARS-CoV-2, the death toll would have been much higher. Georg Schmidt, chairman of the Working Group of Medical Ethics Committees in Germany, is of the opinion that one can consider conducting a HIS only if the risk is manageable and a social catastrophe is imminent. This was, according to Mr. Schmidt, not the case in the Covid-19 situation.[10] Not a catastrophe? Peer-reviewed global estimates of excess deaths indicate 18.2 million people may have died because of the COVID-19 pandemic until 31 Dec 2021.[11] The global Corona pandemic was a catastrophe, especially for the most vulnerable members of society. In addition to the millions of deaths and long-haul Covid cases we should not forget all the liberty rights restrictions due to lockdown measures, and the lost livelihoods due to economic depression. Undoubtedly, the sheer size of a catastrophe matters. The more a pathogen poses an existential risk to humanity or its potential, the more HIS are justified. In a scenario in which a new pandemic would put not millions, but billions of people at risk, many more ethicists would throw overboard their concerns.

2. Benefits of HIS for vaccine research with regard to vulnerable subgroups

The best possible design of vaccine trials, including how many sequential trials there should be, varies from pandemic to pandemic. However, the tendency is that HIS can generate extremely important data for vaccine development. In the case of the SARS-CoV-2 pandemic, the objection to HIS was that the data obtained in young, healthy volunteers could not be transferred to the vulnerable group of people over 70. The WHO disagrees: "Prioritizing the safety of participants is standard in modern challenge studies and acceptable in so far as studies with low-risk participants nevertheless produce useful results (for example, that would help to identify the most promising vaccine candidates or validate correlates of protection)."[12]

3. Health risks for the test persons

The lower the health risks associated with HIS, the more likely they are to be ethically permissible. A specific assessment is always required. In the case of SARS- CoV-2, there were still many uncertainties in the initial phase regarding the pathogenicity or lethality of the virus. There were also no effective drugs or therapies against SARS-CoV-2 in 2020-2021. Unlike, for example, malaria, influenza, typhoid and cholera – diseases for which controlled infection studies have been and are being conducted. The WHO states: "Challenge studies have a long history, including early research with smallpox, yellow fever and malaria that changed the course of global public health. In the last 50 years, challenge studies have been performed safely in tens of thousands of consenting adult volunteers under the oversight of research ethics committees. These studies have recently helped, for example, to accelerate the development of vaccines against typhoid and cholera, and to determine correlates of immune protection against influenza." [13]

Generally, the risks to the subjects are reduced when there is excellent diagnostics so that action can be taken within a sufficiently long incubation period before the disease becomes life-threatening. This was not the case with SARS- CoV-2. And as there was no effective therapy, the health risks for HIS test persons in early 2020 were high.

But it should be noted that in any case there are ethical dilemmas in vaccine development. This is because when HIS are not used, tens of thousands of people must be involved in the phase 2 and phase 3 which then become necessary. And the much larger numbers alone may cause harm to subjects or third parties. In the phase 3 trial to develop Moderna's mRNA-1273 vaccine, 15,210 people received the drug and the same number received a placebo. 30 study participants in the placebo group became seriously ill, and one person died.[14] The WHO emphasises: "Although challenge studies involve the additional risk associated with being infected with a challenge strain (compared to vaccine field trials, which do not increase the probability of infection), it is ethically salient to assessments of risk that challenge studies involve fewer participants, who are more closely monitored and provided with immediate treatment." [15]

The comparison between the risks of phase 1-participants and HIS-participants is of particular interest. To be able to draw analogies, one real phase 1 study during the process to SARS-CoV-2 vaccine testing is explained in detail in the box below:

[10] Reich 2021.
[11] Wang 2022.
[12] WHO 2020: 14.
[13] WHO 2020: 2
[14] Baden et al 2021: 403.
[15] WHO 2020: 6.

How such a phase 1 study proceeds is now described using the example of CVnCoV, the vaccine candidate of the Tübingen-based manufacturer CureVac AG. This study began in June 2020, about six months after the outbreak of the pandemic, at the University Hospital of Tübingen. This clinical trial had been assessed favourably by an ethics committee and approved by the responsible national regulatory authority (the Paul Ehrlich Institute).Volunteers aged between 18 and 60 years (divided into two age groups) from Tübingen and the surrounding area were sought through various channels, e.g. an email to all members of the University of Tübingen, for 2 vaccination appointments and 10 control appointments within a period of 13 months. Compensation of 126,50€ per visit was offered. There was no reimbursement of travel costs or time spent. Personal data was anonymised; a data safety monitoring board supervised data protection.[16] The participants were insured, the (theoretical) maximum insurance sum per participant was 500,000€. It was (for the most part) a double-blind study, i.e. neither subjects nor doctors knew who received the active agent and who received a placebo. In the end, 245 volunteers took part in the study – in Tübingen and at three other centres – and were injected with CVnCoV or a placebo. The dosage of the active agent was gradually increased so that 47 people received 2µg, 48 people 4µg, 46 people 6µg; 44 people 8µg, 28 people 12µg and 32 people the placebo.[17] Phase 1 trails focus on safety/tolerability and immunogenicity. Since the aim is to stimulate the immune system, vaccination reactions are naturally to be expected. At the same time, severe damage to health should be prevented at all costs.[18] One must therefore distinguish between different types of adverse events (AE).Solicited local and systemic AE[19] are expected and no reason for concern. They are accurately recorded in a diary up to seven days after vaccination. *Un*solicited AEs (which hopefully do not occur) are monitored until 28 days after vaccination. In addition, it is checked whether AESI (adverse effects of special interests) occur. For each dosage group, there was a 'sentinel cohort' of two participants in each of the two age groups who received an 'open- label' vaccination, i.e. they were aware that they were vaccinated with the active agent. After assessing the 24-hour safety data of the sentinel cohort, the supervisory committee approved the continuation of the study. This sequential approach was intended to ensure that the study could have been stopped immediately if serious adverse health effects had been observed in the first subjects. Later in the study, the other participants were kept under medical supervision for four hours before being allowed to go home. Each subject received two doses of the vaccine (or placebo), one on their first day and the second on the 29th study day. All solicited AEs were classified according to severity as grade 1 (mild), grade 2 (moderate) and grade 3 (severe) using the FDA scale.[20] Table 1 displays the results with regard to solicited AEs, unsolicited AEs and AESIs:

[16] Kremsner et al. 2021a: 932. "The study was monitored by an internal safety review committee (iSRC) and a data safety monitoring board (DSMB)."
[17] Kremsner et al. 2021a: 932.
[18] There were individual cases of severe health damage in 'first in human' studies in medical history, cf. Attarwala 2010.
[19] Local: pain at the injection site, redness, swelling and itching. Systemic: headache, fatigue, chills, muscle or joint pain, nausea/vomiting and diarrhoea.
[20] US Department of Health and Human Services, Food and Drug Administration (FDA) 2007.

Table 1: Unsolicited Adverse Effects (AEs), Serious AEs, Medically Attended AEs and AEs of Special Interest

	Relation-ship	2 µg	4 µg	6 µg	8 µg	12 µg	Placebo
	N =	47	48	46	44	28	32
Unsolicited	*Any*	*22 (47)*	*32 (67)*	*29 (63)*	*28 (64)*	*21 (75)*	*14 (44)*
	Related	7 *(15)*	19 *(40)*	15 *(33)*	18 *(41)*	12 *(43)*	4 *(13)*
SAEs	*Any*	*3 (1.2)[a]*					
	Related	*0*					
Medically attended AEs	Any	2 *(4.3)*	1 *(2.1)*	4 *(8.7)*	3 *(6.8)*	4 *(14.3)*	6 *(18.8)*
AESI	Any	0	0	0	0	0	0

Italicised numbers are percentages
[a]The 3 unrelated SAEs are not shown by group to maintain blind for this interim analysis

Source: Kremsner et al. 2021a: 934.

The three SAEs were classified as unrelated. It was obvious that these cases – one of which was, for example, a broken arm in a bicycle accident[21] – were not caused by the vaccination. In order to keep a complete account, they are nevertheless recorded in the study protocol. The conclusion of this phase 1 safety/tolerability study of CVnCoV, according to the project leader, Peter Kremsner: "There were no vaccine-related serious adverse effects for the participants. Dose-dependent increases in the frequency and severity of solicited AEs were mainly mild or moderate and of transient duration"[22] This pleasing result was probably not recorded in all of the more than one hundred 'first in human' studies conducted in the 2020 race for the best vaccine to protect mankind against SARS-CoV-2.[23] Many of the vaccine development projects that were undertaken in 2020 were terminated when their unsolicited AEs were too severe.

Final ethical assessment

One can only make serious ethical judgements about empirical facts after one has properly understood them. The case study about organisation of phase 1 trials show that everything is done to protect volunteers from serious harm. But severe illnesses or even deaths are always possible. Nevertheless, ethicists have never objected to this kind of trials – as they are the lesser evil compared to having vaccines too late or not having them at all while a pandemic is raging. This sheds light on the ethical evaluation of HIS. In both cases, phase 1 trials and HIS, the financial compensation of subjects is of relevance for the final ethical assessment. In HIS, the subjects can become contagious after being infected with the virus, therefore there is the need to quarantine them for two weeks minimum. If one only reimburses loss of earnings for this time, one arrives at sums that invite polemical reporting. And unfortunately this really happened as the following case shows:

In England, during the Corona pandemic, there was a HIS to find out what is the minimum viral load that can lead to infection. So the goal here was not to directly accelerate vaccine development. Rather, the study goal was to find out what is the smallest possible amount of virus that can cause Covid-19 disease.[24] The study was commented on in a ZEIT article as follows: "5,770 Euros please? Great. All you need is 17 days of time. You get your own room, a comfortable bed, video games, books, three meals a day and ideal medical care. And yougetinfectedwith Corona."[25]

[21] Kremsner et al. 2021a: 935.
[22] Kremsner et al. 2021a: 932.
[23] A list of projects is continuously updated by WHO: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
[24] Gallagher 2021.
[25] Reich 2021.

To avoid this kind of polemic, I think it would be best to pay for accommodation and meals during isolation time, but refrain from paying any more compensation or an honorarium. Since monetary incentives (including for kidney donation, etc.) are more attractive to poorer people than to wealthier people, there is no real free choice. Given the great willingness to end the Corona pandemic as quickly as possible by participating in vaccination studies, enough volunteer participants would have been found. [26]

Let us assume (counterfactually) that HIS would have taken place during summer 2020 to speed up vaccine licensure. It would have been mandatory from an ethical point of view to provide excellent care for Covid-19 treatment, including priority for any scarce life-saving resources, in state-of-the-art facilities.[27] In concrete terms, this would have meant that scarce resources, e.g. for the drug Remdisivir or artificial lungs, would have been kept ready for this group.

According to Shah et al, "for SARS-CoV-2 controlled human infection studies to be ethically permissible, risks to participants, study personnel, and third parties should be minimized, reasonable in relation to the social value of the research, and below the upper limit of acceptable risk."[28] It is debatable if one should go one step further to protect the health of the HIS subjects. The very idea of phase 1 trials of Biontec, Moderna, AstraZeneca and other companies was to test efficacy of their vaccine candidates (next to tolerability). In the CVnCoV case study described above, as hoped, the antibodies against the spike protein (iGG) in the test persons' bodies rose sharply up to 10,000.[29] It could be assumed that the subjects of the described phase 1 study (apart from the placebo group) had a certain individual vaccination protection as of August 2020.

Now imagine that only those few people that were somewhat protected against Covid-19 would be admitted for human infection studies (if they volunteered) – without installing an 'unvaccinated' control group. Scientifically usable data could be collected from such a HIS even if the establishment of a placebo group was completely dispensed with. The medical-scientific gain in knowledge would then not be as high as it could be. But it would still be many times higher than in the current procedure, where tens of thousands of people are recruited and then wait for a few in both subgroups to become infected.

Another important criterion would have been the 'informed consent' of the test persons. De facto, at least a basic virological-medical knowledge is necessary to be able to calculate the personal risk. Altruism, as commendable as it is, must be supplemented with knowledge. A written or oral test would have been the best way to check whether the test persons had really acquired a certain basic knowledge. But what if, in the case of a new virus, there are still no corroborated facts on pathogenicity (and thus on risk)? The test persons can also give their consent to participate in an HIS in which medicine or science does not yet know many variables. This only needs to be clearly communicated. With regard to the SARS-CoV-2 pandemic, it was known in the summer of 2020 that the virus triggers a much more severe course of disease in older people than in younger people. But many details were still unknown.

All in all, human autonomy should be the deciding argument. In particular, it is incomprehensible why our society legally allows phase 1 trials in vaccine development, but not subsequent human infection trials. As made clear in the case study below, the phase 1 trial subjects also take a risk.As long as someone can assess the risk to themselves, they should be allowed to act altruistically, even at the risk of their health or even their life.

It remains to be stated that no general judgment is possible about HIS to accelerate vaccine developments or approvals. In the case of SARS-CoV-2, the author considers it justified in retrospect, but this ethical judgment has no anticipatory effect on the next pandemic, when circumstances may again be quite different.

In any case, there should be a more open debate than before. The autonomy argument probably justifies human infection studies in more pandemic and endemic situations than previously assumed; there is again no obligation of hospitals etc. to provide the infrastructure for this.

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In spring 2020, Tremmel participated in the phase 1 trial of the CureVac vaccine licensure process[30] as a subject and received 8µg of the investigational vaccine (CVnCoV) twice.

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[26] See, for instance: www.1daysooner.org/.
[27] Eyal et al. 2020: 1753.
[28] Shah et al. 2020: 833.
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Lipedema and its Main Characteristics: A Literary Review

By Thaís Amorim Clemente, Tiago Guedes de Oliveira Viana,
Victória Barros Bottaro, Vitória Bernardes & Paula Cardoso Diniz

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Strictly as per the compliance and regulations of:

Lipedema and its Main Characteristics: A Literary Review

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I. Introduction

Lipedema is a chronic and progressive disease, characterized by its abnormal subcutaneous fat tissue distribution, resulting in its excess, especially in the lower extremities, bilaterally and symmetrically; it also presents frequent hematomas due to small trauma injuries. This disease affects almost exclusively women, being that the initial manifestations of this condition commonly appear in phases of hormonal changes, like in puberty, pregnancy, or menopause.[1,2] The major signs of this pathology are the presence of accumulation of body fat in the thighs, legs, and arms; in terms of symptoms, patients often report pain and swelling in the legs. Research made in 2022 by the Instituto Amato revealed that over 12,3% of Brazilian women that participated in this study have lipedema and that the estimates of the prevalence of lipedema in the general population range from 0.006 to 10%. There is a large case of underdiagnosis of this condition due to the lack of instruments and reliable tests for this purpose, therefore, despite being a particular condition, it is often confused with more frequently diagnosed diseases, such as obesity and lymphedema[3].

Nowadays, the complexity and multifactorial character of this pathology have been increasingly highlighted. Besides affecting the body, this disorder also affects the patient's mental state, considering that the symptoms, by causing a visible disproportion between a standard upper body and thickened lower limbs, can negatively affect self-esteem regarding their appearance, in addition to the possibility of physically limiting daily activities. Therefore, the patient's quality of life is drastically reduced. The stigmatization, labeling, and minimization of suffering affect the mental states of patients with lipedema, which makes it difficult to implement effective therapy and increases the level of pain experienced by them.[1,2]

Regarding that, this work aims to discuss the data presented in the literature concerning lipedema, more specifically on its pathogenesis, diagnosis, complications and treatment. After all, there isn't much research on the subject, so this study intends to synthesize the information already produced on the subject.

The authors declare that there is no conflict of interest.

II. Methods

Seven articles from de last five years were selected from de the PubMed database using the keywords: lipedema, pathogenesis, diagnosis and treatment, in English. The filter "free full article" was also applied. Case reports and articles that were not related to the topic were excluded.

The results obtained in the research carried out in the PubMed database using the parameters described in the methodology of this article are listed below. The presentation of results is arranged in a table containing: the year; publication title; journal/source; publication type; author.

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Table 1: Identification of the articles, according to year; publication title; journal/source; publication type; author

Publication Title	Author	Year	Journal/source	Publication type
Lipedema-Pathogenesis, Diagnosis, and Treatment Options	KRUPPA, P.; *et al.*	2020	Deutsches Ärzteblatt International	Article
Standard of care for lipedema in the United States	HERBST, K.; *et al.*	2021	Phlebology: The Journal of Venous Disease	Article
Lipoedema is not lymphoedema: A review of current literature	SHAVIT, E.; *et al.*	2018	International Wound Journal	Article
Update in the management of lipedema	CORDERO, I. F.; *et al.*	2021	International Angiology	Article
Lipedema: A Call to Action!	BUSO, G.; *et al.*	2019	Obesity (Silver Spring)	Article
Lipoedema as a Social Problem. A Scoping Review	CZERWINSKA, M.; *et al.*	2021	International Journal of Environmental Research and Public Health	Article
Translation, cultural adaptation, and validation of a lipedema symptoms questionnaire	AMATO, A. C. M.; *et al.*	2020	Jornal Vascular Brasileiro	Article

Source: Made by the authors

III. Development

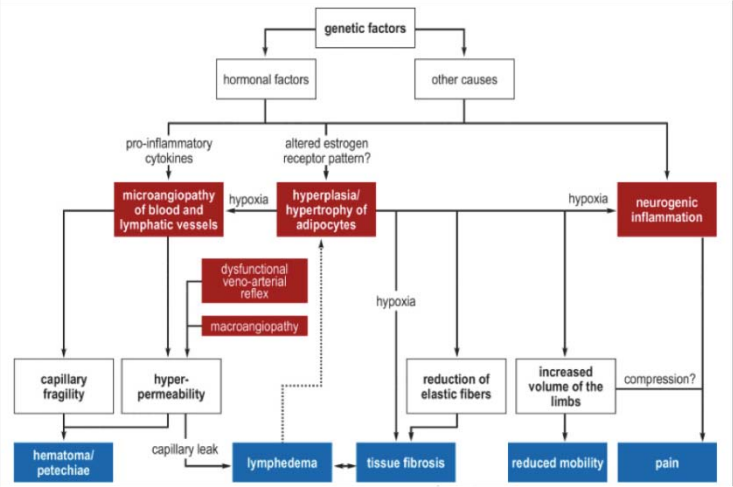
1. Pathogenesis

The pathogenesis of lipedema is not completely clarified. To date, there is still no specific biomarker associated with the onset of the disease, so the diagnosis is made based on the patient's clinic and the exclusion of differential diagnoses.[2] However, some studies have shown that positive family history is present in approximately 60% of patients. Furthermore, changes in the process of adipogenesis, hormonal, microvascular and lymphatic disorders may be related to the abnormal deposition of subcutaneous adipose tissue that characterizes lipedema.[1]

Concerning adipogenesis, previous research has found that in the analysis of the vascular stromal fraction obtained in liposuction of 52 patients with lipedema, there was an increase in the amount of adipose stem cells. Regarding angiogenesis, it was found that patients undergoing shockwave therapy for lipedema had elevated serum levels of endothelial vascular growth factor, suggesting the role of pathological angiogenesis in the development of the disease. Moreover, in non-obese lipedema patients, increased numbers of macrophages, blood vessels and capillary dilation were also verified, which reinforces the hypothesis that changes in microcirculation contribute to the manifestation of the disease.[1]

Another point of investigation is the possible role of genes that suffer the influence of estrogen in the development of endothelial dysfunctions and lymphadenopathies, since it is a fundamental mediator in sympathetic innervation in subcutaneous adipose tissue, in specific areas of the body besides being an important modulator of lipid metabolism, through alpha and beta estrogen receptors, which could explain the higher prevalence of this condition in women. It is also believed that the imbalance of estrogen-mediated weight control mechanisms in the central nervous system may also be related to the accumulation of fat that happens in this pathology. Research has shown that the addition of alpha estrogen receptors in female laboratory rats resulted in hyperphagia and hypermetabolism, suggesting that changes in the estrogen pathway may explain weight loss resistance in patients with lipedema.[1]

Despite the interesting findings of previous research, it is important to emphasize that these are speculative results and without strong scientific evidence, which justifies the need for continuity of studies on the subject, to further elucidate the pathogenesis of lipedema.



Source: KRUPPA, P.; et al., 2021

Figure 01: Flowchart illustrating the pathogenesis of lipedema

2. Diagnosis

As previously discussed, lipedema's diagnosis, due to the lack of specific biochemical markers that can identify the disease, is based mainly on the patient's clinical status and on the exclusion of differential diagnoses, such as obesity, lymphedema, Dercum's disease and chronic venous disease, which are all wrongly diagnosed as lipedema. Besides, due to presenting heterogenic manifestations in different patients, a sound assessment of the patient's history, symptoms, and physical examination is absolutely necessary. The main findings during examination in patients diagnosed with lipedema consist of frail and stretched aspects of the skin, hematomas, disproportional accumulation of fat tissue on the limbs, except for the hand and feet, and also the intensification of symptoms like swelling and sensitivity during the day.[2]

When it comes to the exclusion of differential diagnoses, such as obesity, it is important to emphasize that lipedema is normally influenced by moments of shifting hormonal concentration, such as puberty, menopause and pregnancy, which can help differentiate the pathologies. Furthermore, the preservation of hands and feet of the fat accumulation, less influence of the diet over the symptoms and the associated presence of psychiatric comorbidities are also favorable to it being, in fact, lipedema. However, there are cases of obese patients in which the concomitant presence of lipedema can be elucidated by symptoms such as pain, sensitivity and hematomas, as previously discussed. There are also cases where the diagnosis can only be certain after bariatric surgery because only after a considerable weight loss it is possible to notice the irregular distribution of fat tissue.

On physical examination, it is possible that the doctor will notice the presence of nodules and edema, which increase in size as the disease progresses, in addition to discomfort and pain when performing the Pinch Test, used to assess skin flaccidity. In more advanced cases, lymphedema and a positive Stemmer sign can also be observed (where the examiner is no longer able to squeeze a skin fold in the basal joint of the feet or hands).[2]

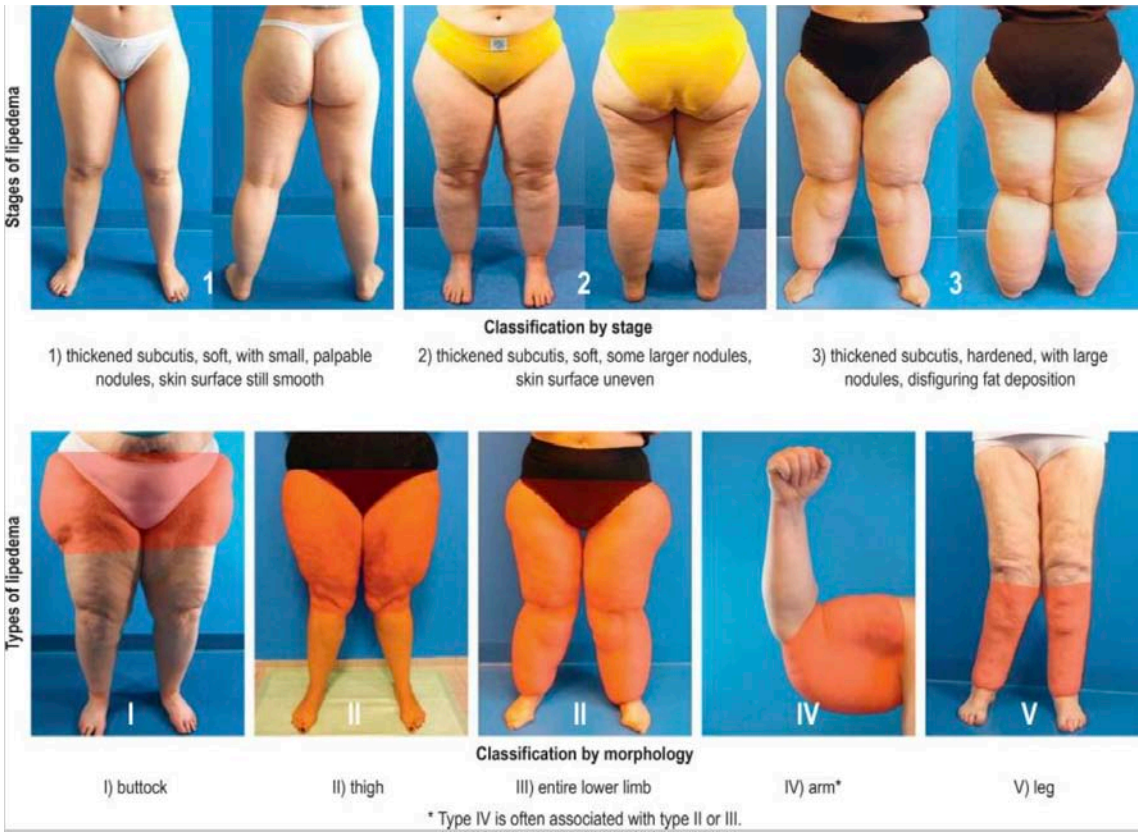
According to the findings of the examination, lipedema can be characterized in three stages:[2,4]

- Stage I: Presence of small nodules, reversible edema, smooth skin with a soft homogenous increase of the subcutaneous tissue, cold skin in certain areas, due to functional vascular imbalance;
- Stage II: Almond sized nodules, reversible or irreversible edema, irregular skin surface, nodular alterations of the subcutaneous tissue;
- Stage III: Deforming fat deposits, macronodular changes, potentially Stemmer sign positive lymphedema, sensitive subcutaneous nodules, a relevant increase of loose skin/tissue circumference, protruding fat mainly on the inner thighs and knees.

Aside from this characterization, this disease can be classified into five different types depending on the location of the fat nodules:[2,5]

- Type I: Affects the buttocks;
- Type II: Affects the buttocks, hips and thighs;
- Type III: Affects buttocks, hips, thighs and calves;
- Type IV: Affects the arms;
- Type V: Affects the calves.

It is important to emphasize that type IV is often associated with types II or III.[2]



Fonte: KRUPPA, P.; et al., 2021

Figure 02: Classification of lipedema according to stage and type

On the other hand, laboratory analyzes are relevant for the investigation of possible differential diagnoses, being common the analysis of liver, kidney and thyroid function, in addition to lipid and glycemic profile. Regarding diagnostic imaging methods, such as X-ray, magnetic resonance imaging and computed tomography, although they allow qualitative and quantitative assessment of the subcutaneous tissue, there is little evidence that demonstrates a great impact on the diagnosis of lipedema, with its most common use in the investigation of differential diagnoses, such as lymphedema.[2]

Lipedema has, in general, a heterogeneous and variable progression, as some individuals may have a stabilization of the disease over time, while others may have a gradual progression. Considering the evolution of lipedema, the most common complaints are orthostatic edema, pain with digital pressure on the affected limbs, hematomas, fatigue and discomfort in the legs. In addition, excess fat in the buttocks, hips, thighs and legs interfere with gait and the misalignment of the mechanical axis of the leg, promoting joint stress that can progress to valgus osteoarthritis of the knee, antalgic gait and/or excessive pronation of the knees. feet. Considering that obesity is a risk factor for lipedema and that women with this disease are at increased risk of developing morbid obesity, it is thought that these patients would have a severe cardiovascular profile. However, according to BUSO et al, fat with gynoid distribution of lipedema correlated negatively with insulin resistance after adjustment for total fat and, consequently, with a less severe cardiovascular profile. This conclusion of cardiovascular risk for patients with lipedema has not been well elucidated.[1] Thus, more concrete studies are needed to clarify more clearly the pathophysiology and complications generated by lipedema.

Lipedema has two treatments recognized by studies and research: conservative treatment and surgery. Lipedema therapy has as its main objectives the relief of symptoms, slowing down the progression of the disease and preventing complications.[6] It is important to emphasize that, currently, there is no known treatment that leads to the cure of this pathology.[2]

Conservative treatment consists of manual lymphatic drainage, compression therapy, physical exercises and diet with weight control, which can be combined with pneumatic compressions, if available.[2,6,7]

Manual lymphatic drainage, compression therapy and physical exercise, together comprise the pillars of therapy to decongest the lymphatic vessels of the affected limbs, stimulating flow and reducing edema. Drainage should be performed regularly and

has been proven to reduce pain and inflammation.[2] Compression therapy should be recommended by the physician and varies according to the degree of presentation of each patient's disease.

Physical exercise should be performed by all those diagnosed with the disease, regardless of the degree of involvement, and the degree of resistance of each individual should be respected.[6] It is important to note that exercises performed in water, such as swimming and water aerobics, are highly recommended, since that the hydrostatic pressure of the water aids in the drainage of the limbs.[2]

The anti-inflammatory diet, despite being a pillar of the conservative treatment of lipedema, does not have published scientific evidence proving the help in controlling the symptoms and the evolution of the disease.[7] However, the nutritional component, seeking to inhibit ongoing systemic inflammation, it is empirically indicated by several professionals who study this pathology.[2] Furthermore, diet as a component of weight control and reduction of total body fat has been shown to be effective in reducing the symptoms caused by lipedema.[6]

Pneumatic compressions can be used to aid conservative treatment to reduce edema and pain in affected limbs.[2,7]

The surgical treatment for this pathology consists of liposuction. Normally, patients undergoing liposuction must have followed conservative treatment for at least 6 months without improvement in their quality of life, that is, with unsatisfactory results.[2] Liposuction in the affected limb would have as main objectives to reduce the evolution of the disease and symptoms of the patient, improving the individual's mobility, reducing the need for compression therapy and lymphatic drainage.[2,7] Currently, the hydroliposuction technique is the most recommended for patients with lipedema, as it reduces damage to the lymphatic tissues.[6]

Liposuction performed for the treatment of lipedema should be performed by a professional with experience in this type of treatment, since the volumes of fat removed will possibly exceed those traditionally recommended. Furthermore, multiple surgical interventions may be required to obtain the desired outcome.[2]

IV. Conclusion

Lipedema is unknown to part of the medical community and commonly confused with some diseases such as lymphedema and obesity and is therefore often underdiagnosed. Its diagnosis is divided into three stages and five types, depending on the area of the affected body. Lipedema can significantly impact the patient's quality of life if not diagnosed early. Several studies prove the importance of treatment, especially conservative treatment, for the evolution of the disease since there is no known cure.

Treatment may involve manual lymphatic drainages, weight control, an anti-inflammatory diet, compressive stockings and even liposuction of affected areas, depending on the patient's clinical picture. While there are scientific shreds of evidence that corroborate the efficacy of treatment in improving the symptoms of this pathology, its pathogenesis is not yet fully clarified. Further and more extensive studies and research on the subject are still needed to elucidate the pathophysiology better.

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Co-Occurrence of Lichen Planus and Alopecia Areata: A Possible Role of Plasmacytoid Dendritic Cells

By Dr. Harshita Sharma, Dr. Madan Mohan, Dr. Shilpashree P. & Dr. Divya Gupta

Introduction- A 14-year-old female presented with multiple dark coloured, itchy lesions on legssince5 months. On examination, multiple violaceous papules to plaques of varying sizes (1cm - 5cm) were present on the extensor aspects of legs, forearm and dorsum of feet bilaterally. (Figs 1-3).Skin biopsy from the lesion showed hyperkeratosis, hypergranulosis, vacuolar degeneration of basal layer, band of dense lymphocytic inflammatory infiltrate in the papillary dermis, with perivascular histiocytic infiltrate confirming the diagnosis of lichen planus (LP) (Fig 4,5). She was started on topical corticosteroids, antihistamines and emollients. After 3 months patient had aggravation of LP with patchy hair loss over the scalp. On examination multiple, smooth alopecic patches of varying sizes, the largest being 4 x 3 cm, were noticed on the scalp. She was diagnosed clinically as alopecia areata (AA) (Fig 6). Investigations like complete blood count, liver function test, thyroid profile, anti-nuclear antibody, rheumatoid arthritis factor, C-reactive protein, ESR, VDRL, HBV, HCV, urine microscopy were normal. In view of progressing lesions of LP and AA, she was started on oral mini pulse therapy-betamethasone 5 mg twice weekly and was advised for follow – up. Good response was noticed by four weeks with resolution of LP and regrowth of hair over few patches.

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Co-Occurrence of Lichen Planus and Alopecia Areata: A Possible Role of Plasmacytoid Dendritic Cells

Dr. Harshita Sharma [α], Dr. Madan Mohan [σ], Dr. Shilpashree P. [ρ] & Dr. Divya Gupta [ω]

Introduction

A 14-year-old female presented with multiple dark coloured, itchy lesions on legssince5 months. On examination, multiple violaceous papules to plaques of varying sizes (1cm - 5cm) were present on the extensor aspects of legs, forearm and dorsum of feet bilaterally. (Figs 1-3).Skin biopsy from the lesion showed hyperkeratosis, hypergranulosis, vacuolar degeneration of basal layer, band of dense lymphocytic inflammatory infiltrate in the papillary dermis, with perivascular histiocytic infiltrate confirming the diagnosis of lichen planus (LP) (Fig 4,5). She was started on topical corticosteroids, antihistamines and emollients. After 3 months patient had aggravation of LP with patchy hair loss over the scalp. On examination multiple, smooth alopecic patches of varying sizes, the largest being 4 x 3 cm, were noticed on the scalp. She was diagnosed clinically as alopecia areata (AA) (Fig 6). Investigations like complete blood count, liver function test, thyroid profile, anti-nuclear antibody, rheumatoid arthritis factor, C-reactive protein, ESR, VDRL, HBV, HCV, urine microscopy were normal. In view of progressing lesions of LP and AA, she was started on oral mini pulse therapy-betamethasone 5 mg twice weekly and was advised for follow – up. Good response was noticed by four weeks withresolution of LP and regrowth of hair over few patches.

LP and AA are autoimmune dermatoses and are associated with other conditions like diabetes mellitus, vitiligo, autoimmune thyroid diseases etc to name a few.So far, only 3 reports of co-localization of AA and LP have been published in the literature.[1-3] Till now, no case report of coexistence of LP and AA has been reported. Plasmacytoid dendritic cells (pDCs) are specialized dendritic cells exhibiting plasma cell morphology, expressing CD4, CD123, HLA- DR, blood-derived dendritic cell antigen-2 (BDCA-2), Toll- like receptor (TLR)7 and TLR9 within endosomal compartments and their role in autoimmune diseases is gaining traction recently. On activation, they produce type I IFN, against pathogenic agents and link the innate and adaptive immunity by controlling the function of myeloid dendritic cells, T, B and natural killer cells. pDCs are absent in normal skin but infiltrate when injured, thereby contributing in the pathogenesis of inflammatory dermatoses (like LP and AA). Vries et al found pDCs in close approximation to basal layer in lesional LP, corresponding to lymphocytic infiltration.[4] It has been hypothesized that some common antigenic determinant may be a triggering factor for onset of both diseases, and thus, a primary autoimmune process directed against basal epidermal cells in LP could have possibly resulted in disruption of hair follicle immune privilege zone thereby exposing the hidden antigens from hair follicles, leading to pDCs recruitment, production of IFN-gamma and resulting in aggravation of LP and occurrence of secondary autoimmune response i.e., AA.[5]

This explains the coexistence of LP and AA in our case report. This rare case of sequential occurrence of LP followed by AA has not been reported previously and might offer possible theories which contributes to the literature of T cell mediated autoimmune disorders.

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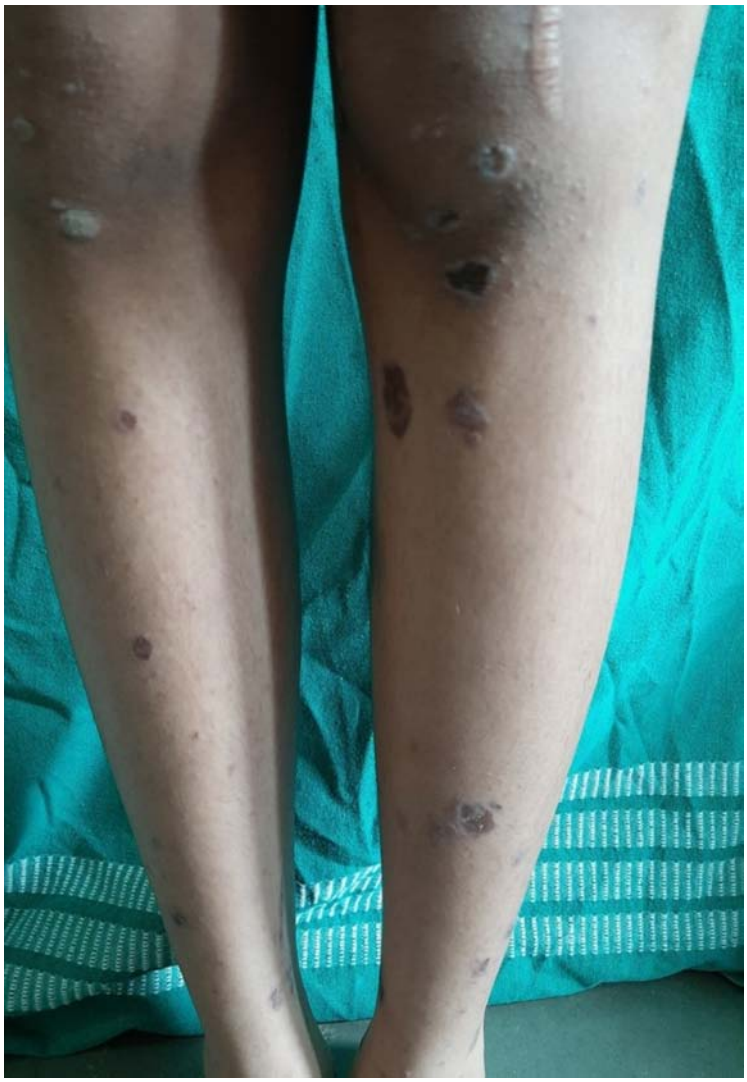

Figure 1: Multiple violaceous papules to plaques of varying sizes over the extensor aspects of both legs bilaterally.

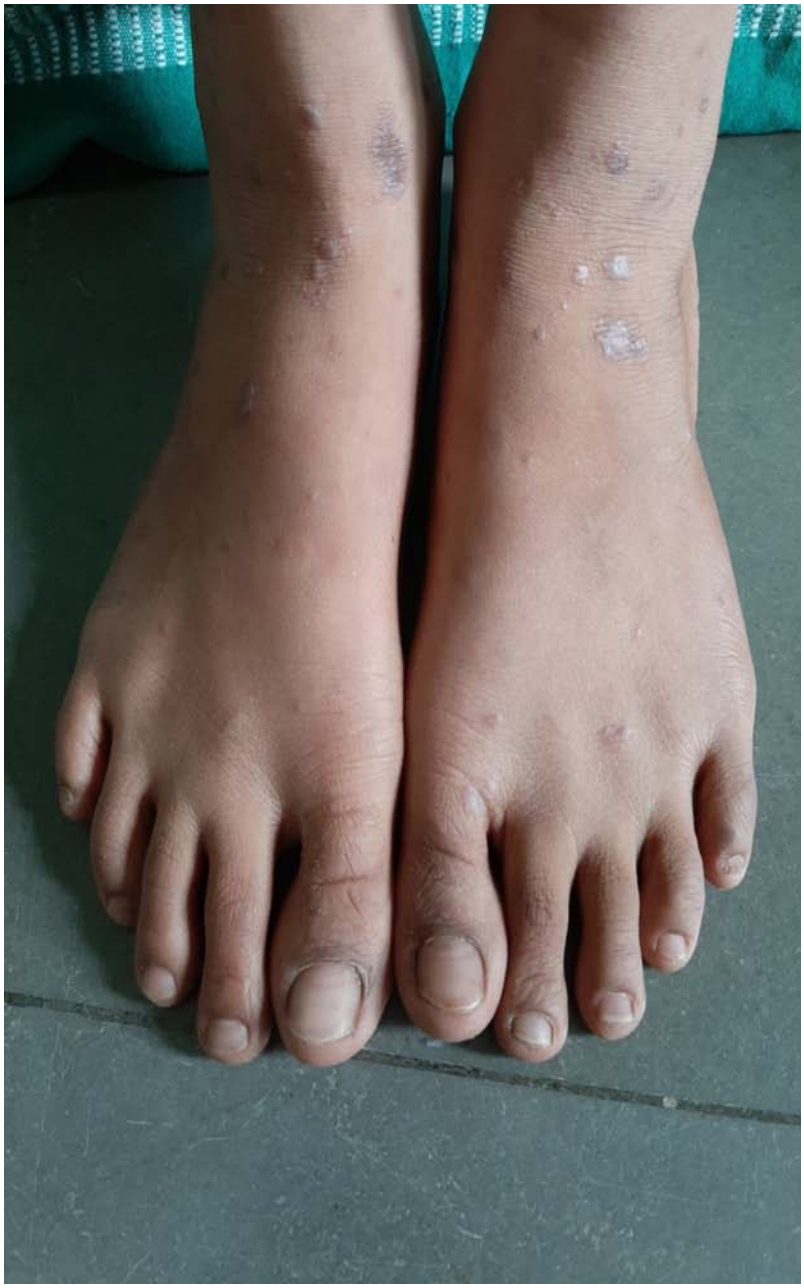

Figure 2: Multiple violaceous papules to plaques over the dorsum of feet bilaterally.

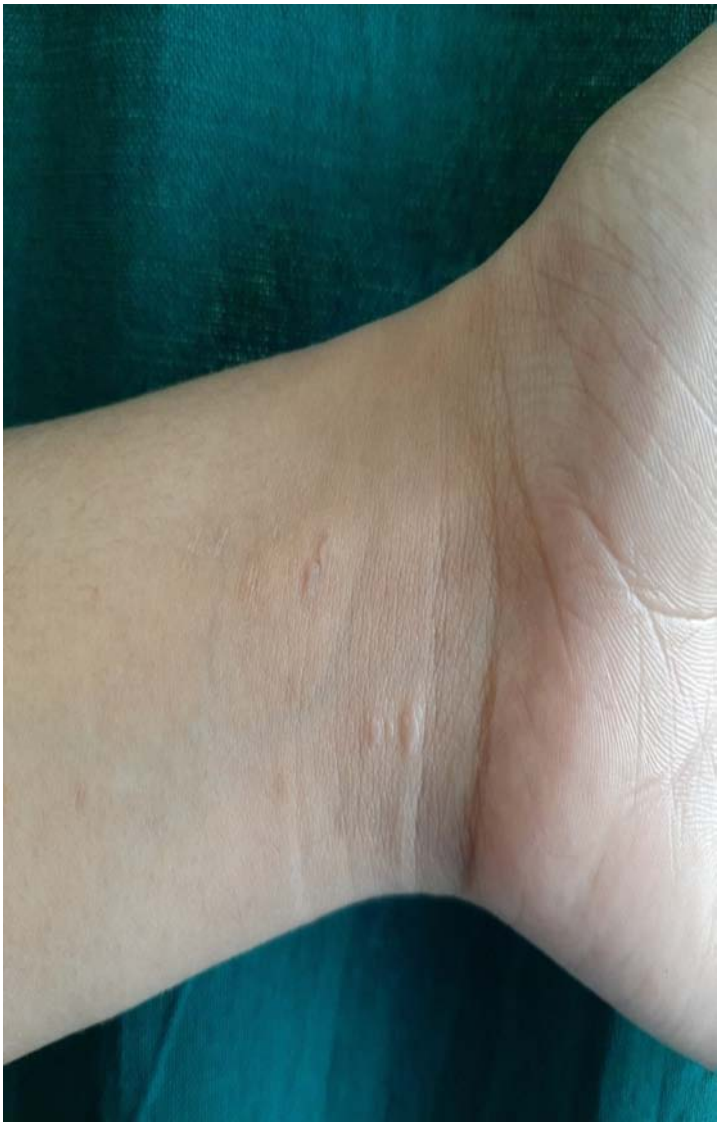

Figure 3: Few erythematous papules over the wrist area.

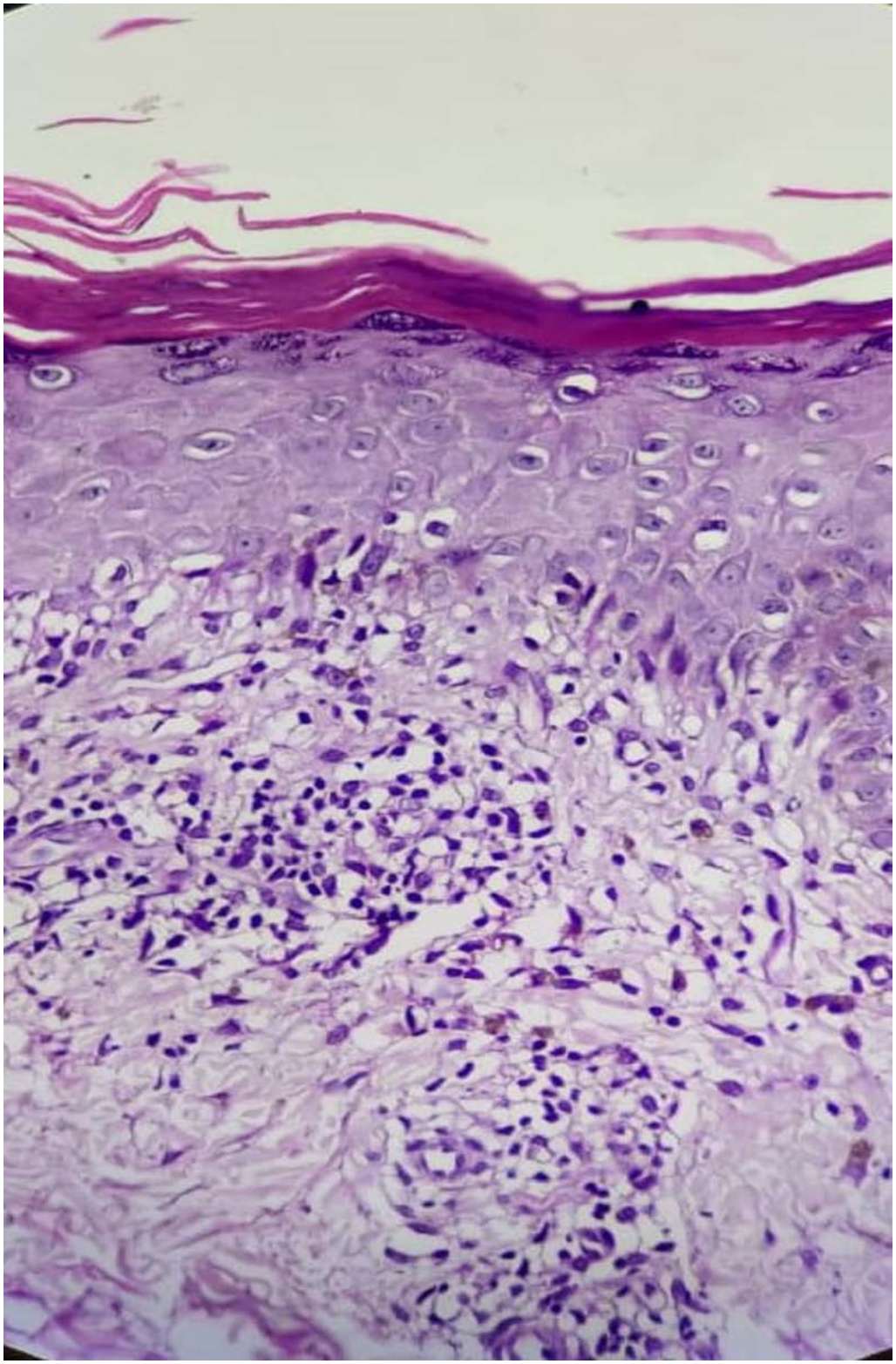

Figure 4: Photomicrograph showing hyperkeratosis, parakeratosis, hypergranulosis, band of dense lymphocytic inflammatory infiltrate, histiocytes admixed with congested blood vessels, along with periadnexal inflammatory infiltrate. (H & E, x 40).

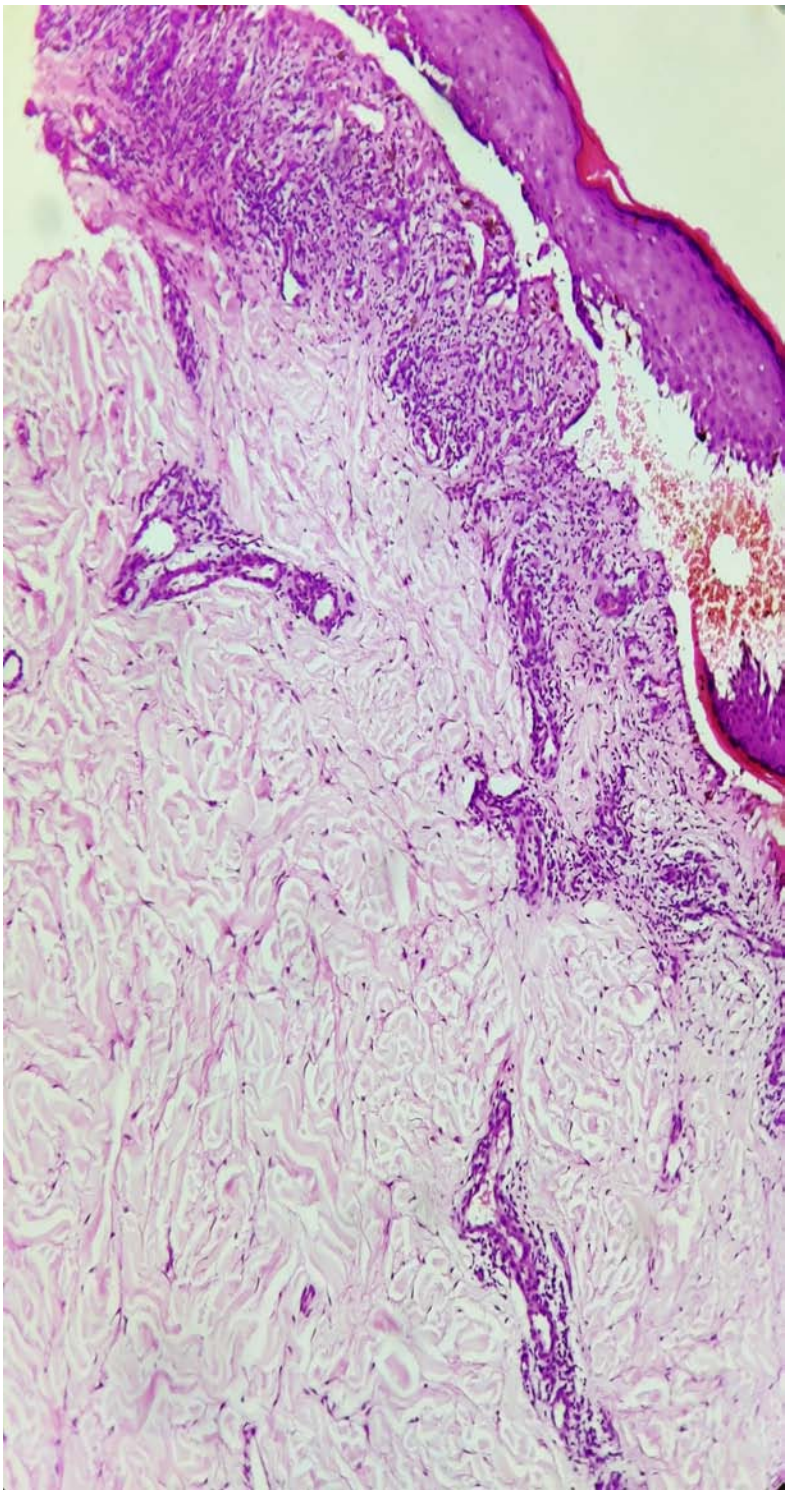

Figure 5: Photomicrograph showing hyperkeratosis, parakeratosis, hypergranulosis, artifactual cleft formation between epidermis and papillary dermis (Max Joseph space), band of dense lymphocytic inflammatory infiltrate, histiocytes admixed with congested blood vessels, along with periadnexal inflammatory infiltrate. (H & E, x 10).

Figure 6: Multiple well demarcated, smooth, bald, round alopecic patches of hair loss of varying sizes on the scalp.

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Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

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Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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