

# **The effect of Proinsulin C-peptide on HRV and the LF/HF rate**

## **Prospective study**

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## Preface

Heart Rate Variability (HRV) is an indicator of the balanced functioning of the brain.

When we take a breath and inhale, our heartbeat accelerates, when we exhale, it slows down. Heart Rate Variability (HRV) measures the dynamic change of this process. The more evenly our heart beats, the greater the problem may be with the complex function of regulating heartbeat in our central nervous system. But also too high HRV value may refer to health problems, arrhythmia. Researchers relate the general health status mainly to the HRV value measuring the functioning of the vagus nerve. Diseases like diabetes, cancer, arteriosclerosis, schizophrenia, autism, Alzheimer's and Parkinson's disease, etc. are often related to lower HRV values. Since it is mostly the healthy functioning of the prefrontal cortex that is in charge of the HRV values, the integrity of brain functions determine and influence the incidence of the different chronic diseases.<sup>i</sup> The particular values of HRV are in connection with the extent of inflammatory processes in the body, the lower these values are, the higher certain inflammatory markers may be.<sup>ii</sup> The so-called cholinergic anti-inflammatory pathway is in charge of the anti-inflammatory effect of the vagus nerve. The impairment of the vagus nerve system and the increased inflammation due to that also predicts the eventual early death.<sup>iii</sup>

Researchers correlate the impairment of the cholinergic anti-inflammatory pathway with the emergence of respiratory failure due to COVID-19 infection especially in cases with the comorbidity of e.g. Alzheimer's disease or unhealthy lifestyle.<sup>iv</sup> Researchers even defined a limit in the value of RMSSD, the HRV transmitted by the vagus nerve, below that the chance of developing chronic diseases, such as cardiovascular problems is significantly increased.<sup>v</sup>

In this regard it is a cause for concern that children suffering from type 1 diabetes mellitus, where the total or partial lack of insulin and of the other associated peptide, proinsulin C-peptide is typically observed, HRV is significantly reduced.<sup>vi</sup>

Researchers state that this may be primarily due to the glycemic control, but the glycemic control is the best in those patients with type 1 diabetes, whose residual C-peptide production is relatively high.<sup>vii viii ix</sup>

It is worth mentioning that adding supplementary C-peptide significantly raises the low HRV value in patients with type 1 diabetes mellitus.<sup>x</sup>

Regarding the patients in concern raised HRV may certainly be the result of the effect of proinsulin C-peptide on the central nervous system, despite the fact that the transfer of C-peptide through the blood-brain barrier is 5 times lower than the transfer of insulin.<sup>xi</sup>

In animal experiments the effect of c-peptide regarding the activation of the vagus nerve, administered directly into the brain, avoiding the blood-brain barrier, was the same in much less quantities than in systemic dosages.<sup>xii</sup>

In the future the idea of therapeutic application of proinsulin C-peptide may arise in people with chronic diseases due to its effect on raising and optimizing HRV and eventually regenerating brain functions, especially because it can easily and effectively get into the

central nervous system through intranasal administration, avoiding the blood-brain barrier.<sup>xiii</sup>

## **Introduction**

More than 2 years ago cosmetics containing proinsulin C-peptide became available in trade flows for the first time in the world. For a number of people this made it possible to use it off label, as a nasal spray, similarly to intranasal insulin. The experiences gained during these two years are astonishing and surprising. In our case study primarily the effect of C-peptide on HRV is analyzed, which is an indicator of the parasympathetic system of the body.

**HRV, RMSSD, LF/LH rate were measured by Elite HRV equipment.**

### **HRV value**

HRV value is the responsiveness of the heart, it means the emotional, hormonal and neurological balance of the whole person, as well as the reactivity in life situations. The higher heart rate variability, that is HRV, is a complex measure of health. It describes how the heart can constantly change the period between two heart beats while reacting to the changing loads of the internal and external environment. The adaptive ability of the heart is based on the optimal interplay of the sympathetic and parasympathetic nervous system. Adequate heart rate variability can be achieved in the body if the two systems are in balance. If the sympathetic system starts predominating, HRV is going to decrease. This in turn will increase the risk of developing cardiovascular diseases.

The HRV and RMSSD values change with age. Both too high and too low HRV may refer to health problems. It can also be said about HRV, that it reflects the health state of the brain as well.

When analyzing the results we used the chart of the Elite HRV equipment, the ideal range concerning age was defined according to those values.

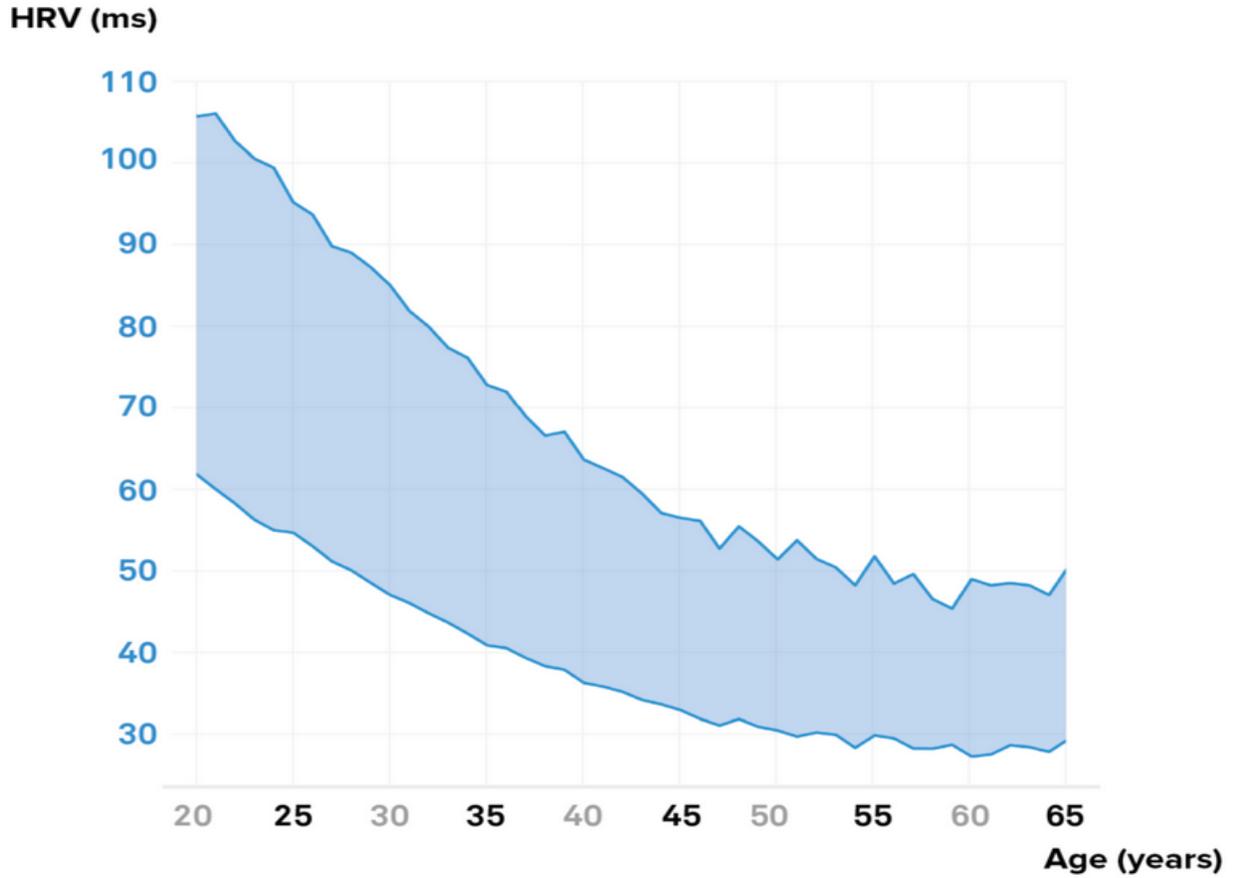


Figure 1 - Mean HRV depending on age

Mean HRV depending on age

Age	Sex	RMSSD	Elite HRV
18-25	Male	86.5	68.7
	Female	68.7	65.1
25-35	Male	66.0	64.5
	Female	55.7	61.8
35-45	Male	50.4	60.3
	Female	45.6	58.7
45-55	Male	39.6	56.7
	Female	41.7	57.4
55-65	Male	32.1	53.3
	Female	32.5	53.5
65-75	Male	30.6	52.7
	Female	24.8	49.4
75+	Male	33.1	53.9
	Female	25.5	49.9

## **LF/HF rate**

The LF range is primarily determined by the sympathetic system. The LF value reflects the sympathetic and parasympathetic values in a rate of 3:1 (three-quarters sympathetic, one-quarter parasympathetic). The raised sympathetic activity may be caused by lack of sleep, stress or sickness.

The HF range is affected by the parasympathetic activity.

The LF/HF rate refers to the vegetative balance. The optimal value is 1.5-2 ( $ms^2$ ). If the value is lower than this, there is a parasympathetic, if higher, than a sympathetic prevalence.

## **Description of the proinsulin C peptide spray**

The participants of our study were using the Vargapeptide skin-spray off label, as an intranasal spray, on their own responsibility. The spray is produced and distributed by the Max-Immun Ltd.

This was applied in the same way as the intranasal insulin was and is administered in the population of children with Phelan-McDermid syndrome.

A 20 ml bottle contains a solution of 18 ml C-peptide. One puff of the spray contains 0,108 mg proinsulin C-peptide. In Varga Peptide 0,5 this amount is half of it, 0,05 g, in Varga Peptide 2 the amount is 0,216 mg. The spray contains 0,8 % NaCl. The other ingredients fulfill the requirements of pharmaceutical grade purity. The purity of proinsulin C-peptide is 98-99%.

## **Description of the investigation**

### **Selection**

The participants of the study were selected in May 2020.

The first assessment consisted of an initial measurement and a survey using a questionnaire

### **The schedule of the measurements:**

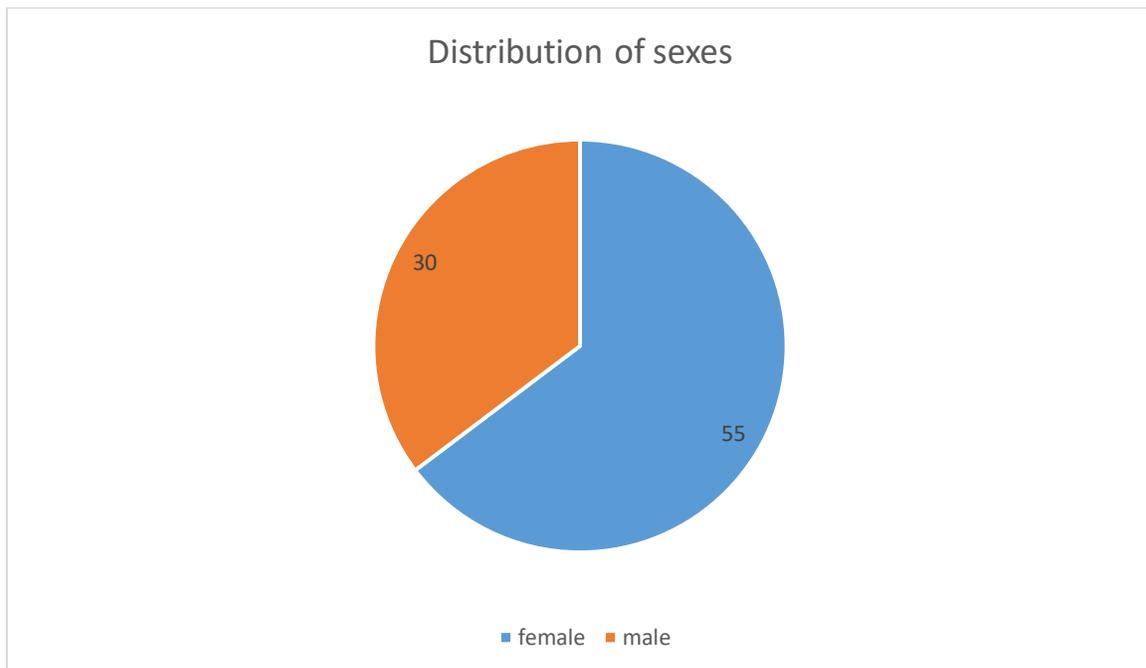
1. initial measurement
2. after one week
3. after one month
4. after 3 months
5. after 6 months

## Statistical data

There were 85 participants in our investigation. Out of these persons 2 patients quit after 3 months, 1 patient could not continue due to the COVID pandemic and 1 patient with chronic diseases died (chronic renal disease, hypertonia), therefore the measurement after 3 months was already impossible to be executed.

The age range of patients was 3-78 years, the average age was 46.85 years.

The distribution of sexes was 30 males, 55 females.



*Figure 2 - Distribution of sexes*

## **Diseases**

The participants of the investigation were not selected according to certain diseases, therefore a wide range of diseases can be found, and also each patient has more than one diagnosis, such as:

Duchenne-syndrome, infantile autismus, moderate intellectual disability, dysgraphia, attention deficit, behavioural disturbance, sensory integration disorder, autismus, myoclonic epilepsy, stroke, balance disorder, vertigo, anxiety, synovitis, scoliosis, hypertonia, ragweed allergy, hypothyreosis, obesity, joint pain, type 2 diabetes mellitus, lung tumor, breast tumor, skin cancer, spinal hernia, cardiomyopathy, colitis ulcerosa, reflux, autoimmune thyroid disease, prostate tumor, speech rhythm disturbance, depression, deep vein thrombosis, gynecological tumor, sleeping disorder, EBV, pollen- and peanut allergy, neurasthenia, facial neuralgia, COPD, vaso-constriction, osteoporosis, dementia, ovarian cyst, hearing loss (80%), metabolic disorder, SIBO (Small Intestinal Bacterial Overgrowth), menopause, food allergy, multiple sclerosis, metastatic breast tumor, Traumatic Brain Injury, renal failure in final stage, benign skin tumor, panic disorder, spastic tetraplegy, perinatal injury, tinnitus, coordination disorder, migraine, Asperger syndrome, low back pain, chronic fatigue, stress, Angelmann syndrome, pacemaker, torticollis, sciatica, pelvic tumor, dementia, earache, nervous exhaustion, Hashimoto thyroiditis, hyperthyreosis, irritability, abdominal pain, nephritis, gravidity, nausea, weakness, fatty liver, arthritis rheumatica, Parkinson's disease, extreme high blood pressure, asthma, Leiden mutation, COVID, colonic tumor, mixed disorder of the connective tissue, psoriasis, mitochondrial disease, Lyme disease, Bell-paresis, ADHD, immune deficit, Conn syndrome, autoimmune hepatitis.

## **Frequency and dosage**

The dosage of C-peptide was started from type 0,5, than 1 and 2, according to age, than the dosage was changed according to the symptoms and the results.

The duration of appliance was 3-6 months.

Patients will continue taking C-peptide after 6 months as well.

## **Aspects of data collection and analysis**

Each time of measurement the patients answered the items of the questionnaire, and the subjective observations were recorded as well.

## Results

There was a great obstacle in the implementation of the investigation: the COVID-19 pandemic, therefore some of the measurement times were changed, and it also happened, that a measurement was skipped due to an infection.

The chart contains the patients' age, sex, diagnosis, measured values and the changes in symptoms according to the questionnaires. The type and dosage of C-peptide is also indicated.

The chart containing the data and results of each patient can be found in the Appendix.

### Changes in HRV and RMSSD

In our investigation the HRV and RMSSD values were the following during the administration of C-peptide:

HRV and RMSSD was in the normal range according to age in 40 patients. In 43 patients both HRV and RMSSD values were low. The HRV and RMSSD values have been changed parallel to the administration of C-peptide.

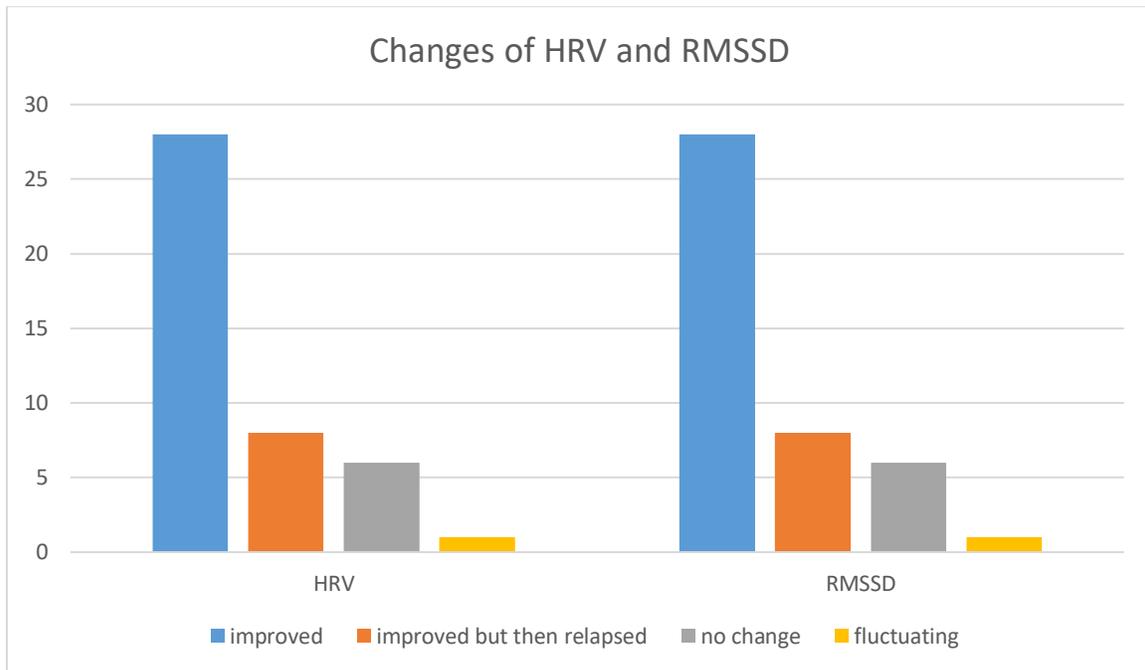
Our measurements have also indicated that the HRV and RMSSD values were significantly influenced by the consumption of coffee, chocolate or cigarettes before the test. Patients under chemotherapy treatment had similar values. COVID infection also negatively affected HRV.

Age Sex	Diagnose	Dosa ge	HRV	RMSSD	LF/HF	Comments
67 Female	IBS pain of unknown origin	0.5 1x1 1x2 2x4 2x6 2x6	67 41 stress 50 46 (coffee, cigarette mask 59 (coffee, cigarette )	80.21 14.44 26.25 19.35 47.73	0.51 8.04 1.08 1.42 2.15	takes several medicine smokes, stressful earlier suffered from herpes, during the investigation none occasional cough stopped d joint paine relieved depression due to COVID worsened, hard for her to cope with the lock down
	6 months					
59 Female	malignant lung and breast tumor	1 2x1 2x2 2x2	52 45 36 (did not take for 4	30.3 18.74 10.53 29.26 22.15	1.72 2.37 4.91 0.98 2.32	takes several medicine, receives chemotherapy smokes after 6 months chemotherapy check-up arm itching remained, numb toes, surgery

			days during chemotherapy) 52 48 (coffee)			after the 2. test she is in healing phase, feels well, joint pain ceased general health better, but feels week due to chemotherapy and radiation therapy
	6 months					
64 Female	Colitis ulcerosa reflux	1 2x2 3x2 2x2	47 53 53 49 stressful smoked 63 stressful	21.52 30.69 30.73 23.46 58.51	6.15 1.21 3.17 1.13 1.17	smokes (less, earlier 1 now half packet,) minor waist pain ceased colitis ulcerosa 1x recurred, had bloody stool for 1 day, (CU since 1977) earlier these episodes lasted for 2-3 weeks if the C-peptide dosage was raised, got mild headache learns easier (e.g. dance choreography) short-term memory improved a bit does not catch infections
	6 months					
60 Female	autoimmune thyroid disease	0.5 1x 2x1 0.5 2x2 1 2x2	60 49 ate sweets 51 52 ate chocolate, stressful	50.56 23.46 26.97 129.63	4.79 1.13 0.45 0.54	smokes 15-16 cigarettes daily, her pulse rises, this did not change  Decreased the dosage of C-peptide because of severe anxiety  After initial improvement a stressy period amplified her symptoms  Very stressful, because her husband got into hospital
	3 months					
70 Female	facial neuralgia, COPD, vaso-constriction, osteoporosis, dementia, depression	0.5 1x 2x1 2x2 2x2	43 59 64 46 ate chocolate, 43 stressful, upset	16.24 46.84 62.29 19.82 16.39	1.52 6.61 1.36 1.4 0.73	takes several medicine smokes reflux got better after 3 months had fracture after 3 months, recovered feels more often cold does not really feel improvement depressed mood, upset
	6 months					

## Changes in HRV

Among the patients having low HRV at the beginning, the values of 28 patients improved due to the administration of C-peptide, in 8 cases there was an initial improvement, but later a relapse was experienced. In the cases of 6 patients there was no significant change. The value of 1 patient was fluctuating.



*Figure 3 - Changes of HRV and RMSSD values in patients with low values at the beginning*

Our observations were in the changes of HRV, that in the initial phase a deterioration often occurred. A HRV változásában megfigyeltük, hogy a kezdeti időszakban előfordul egy rosszabbodás. The time period needed for the improvement to appear was investigated and also the duration of it.

In 16 cases the values started improving already in the first month and these increased values remained all through the time applying C-peptide.

In 5 cases the first improvement was noticed in the 3. months, while in 2 cases the first in the 6. months.

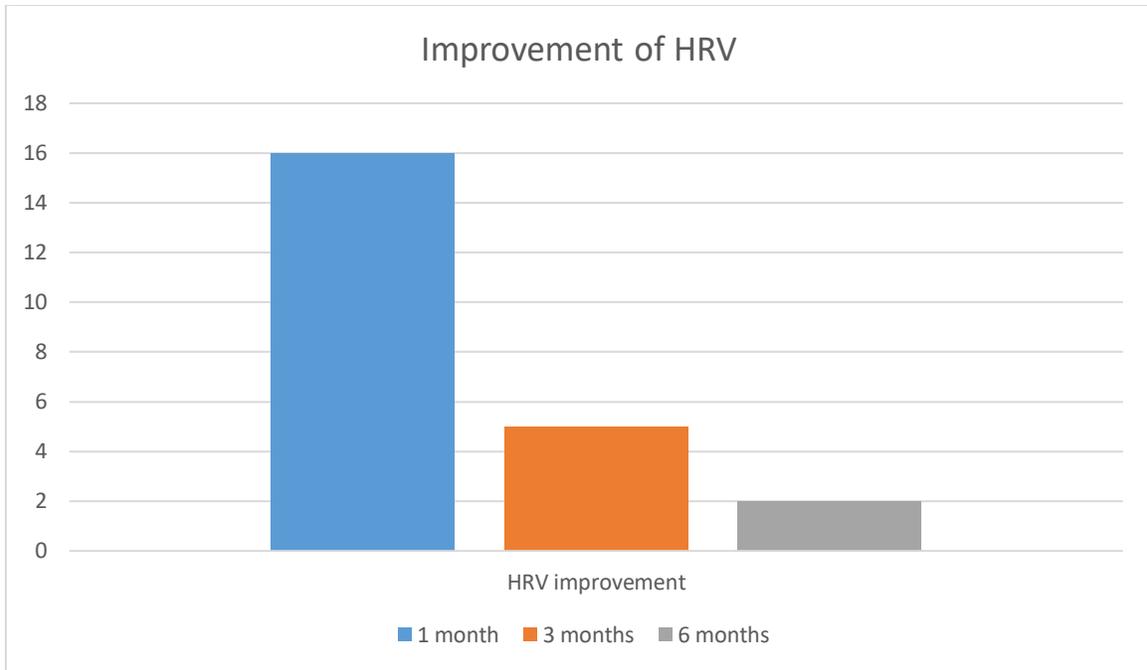
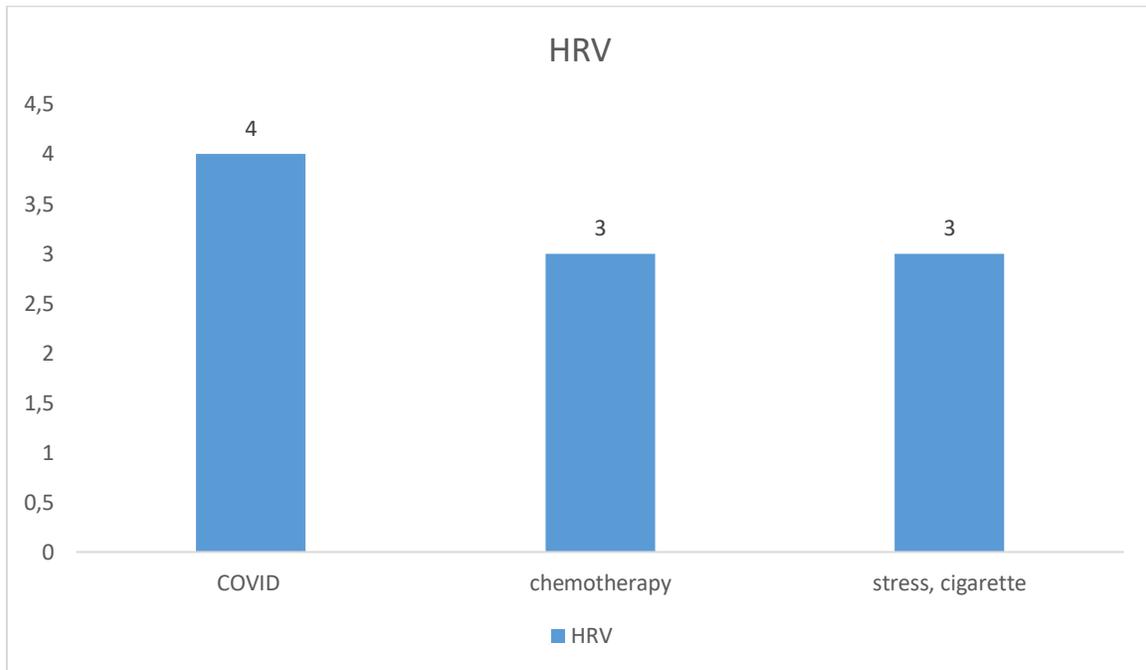


Figure 4 - The improvement of HRV over time

Age Sex	Diagnosis	Dosage	HRV	RMSSD	LF/HF	Comments
3 Male	Duchenne	0.5	61	53.02	0.73	Face redness milder
		1x	68	81.16	1,2	Immune system strengthened
		2x	72	110.01	7.2	Healing faster when catching a cold
		2-3x	72	106.4	0.57	Motor abilities improved a lot, sits up independently lot better adaptation abilities can walk up stairs not disturbed by the vacuum cleaner attention span longer says more and more words

## Deterioration of HRV

In the cases of 10 patients the initial HRV was in the normal range, but when measured later, worse results were found.



*Figure 5 - Deterioration of HRV*

4 patients from these 10 got coronavirus infection.

3 patients received chemotherapy, one of them had improved values after 5 months. Another patient showed improvement in the 3. months, but before the measurement in the 6. month received chemotherapy again and the measured values got worse again. 1 patient received both chemotherapy and radiation treatment.

1 patient felt very stressful, had a coffee before the measurement, wore facial mask, had a really hard time emotionally due to the lock-down of the COVID pandemic.

The values of 1 patient were worse in the 3. and 6. month, he reported to be very stressful, exhausted, works a lot, takes several medicine.

The values of 1 patient got worse in the 5. month, smokes a lot, anxious.

Age Sex	Diagnosis	Dosage	HRV	RMSSD	LF/HF	Comments
59 Female	stiatica, palvic tumor	1 2x2	56 44	37.83 17.24	3.08 4.34	takes several medicine, recovered from COVID within 5 days  chemotherapy, radiation treatment  vitality improved, high pulse Due to covid changed for immunotherapy after 3 months
64 Female	colon tumor, chemotherapy		53 46 49	32.33 19.4 24.2	53 46 49	chemotherapy, medicine fluctuating health feels a lot more forceful
	3 months					
	0-3-5 months					

## Changes in LF/HF

The LF/HF rate was very high in a lot of patients according to our measurements. The changes were not so clear as those of HRV. A lot of patients had really high LF/HF rate, which refers to a dominating sympathetic functioning. The changes of values were also diverse.

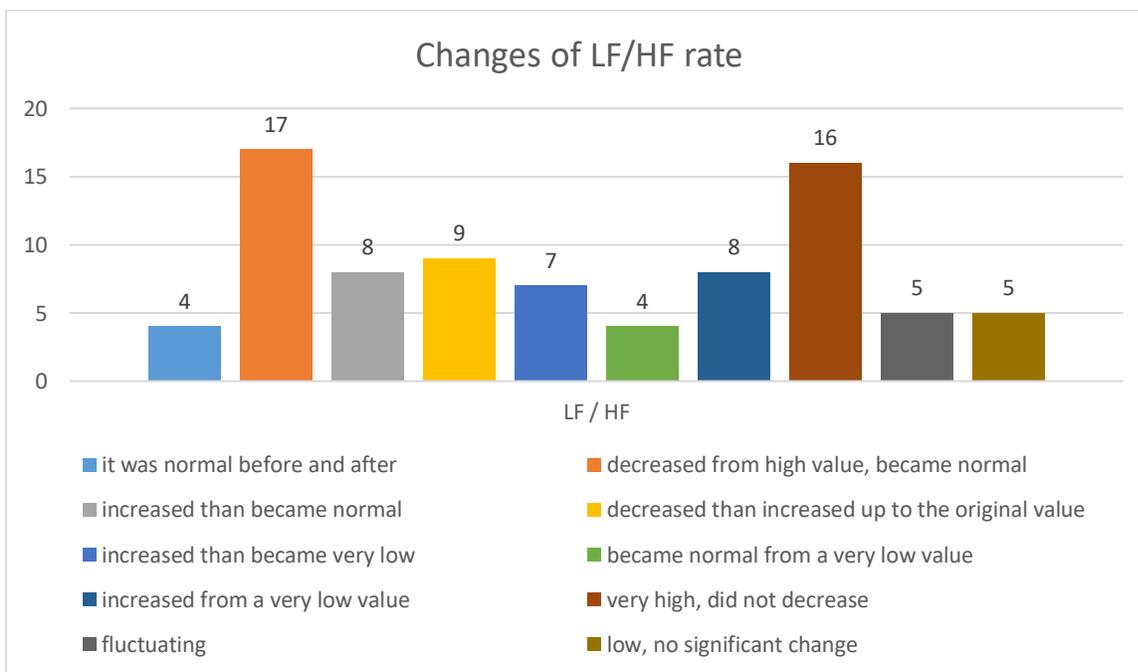


Figure 6 - Changes of LF/HF rate

## **Changes of the LF/HF rate**

The values of 4 patients were in the normal range and remained there as well.

The high values of 17 patients decreased and remained in the normal range while applying C-peptide.

In the cases of 8 patients an initial raising was found, then their values turned to be normal.

The values of 9 patients decreased, then raised back to high values. 2 of them received chemotherapy, 1 was infected by coronavirus, 1 patient had miscarriage, and 1 patient has inflammation in her body.

The values of 16 patients were very high, did not decrease. 5 of them received chemotherapy, 1 person had COVID infection as well, 1 patient receives radiation treatment. 2 patients take a lot of medicine. 3 patients suffer from severe anxiety and depression. 1 is a smoker, 1 has high blood pressure, 1 patient has autoimmune disease and 1 facial nerve palsy, as well as 1 patient has tetraplegia.

In 7 patients first raised, then very low values were experienced. 4 of them take several medicines, 1 got COVID infection, 1 patient was under renal dialysis treatment, and 1 patient developed severe anxiety due to applying C-peptide, therefore the dosage could not be raised.

Very low value, the LF/LH rate below 1 was experienced in 1 patient, low values were found in 2 patients.

The LF/LH rate increased from a very low value, but did not reach the normal range in 8 patients. Interestingly, these patients had frequent herpes infection was found in their medical history.

The values of 4 patients became normal, starting from a very low value, their original diseases were earache, Bell-paresis, torticollis and epilepsy.

5 patients showed absolutely fluctuating values, each of them takes a lot of medicine regularly.

## **Changes depending on the dosage**

The experience of our investigation pointed out that the changes both in HRV and the LF/HF rate dependent significantly on the dosage of C-peptide. In the cases of those patients, where the dosage was slightly or not changed at all, the values did not change. Therefore it is recommended in each case to change dosage according to symptoms and the results of the measurements.

Age Sex	Diagnosis	Dosage	HRV	RMSSD	LF/HF	Comments
58 Female	Hypertension	0.5 2x2	51 49 56 50 60	27.99 24.83 38.94 26.11 48.69	2.62 3.93 2.28 2.26 4.18	blood pressure stabilized in the normal range mood and sleeping improved copes with stressy situations better feels more forceful strain using the power improved a lot
	6 months					
20 Male	Infantile autismus	0.5 2x1	63 68 58 47 49	60.55 82.9 43.54 22.49 24.51	1.65 1.29 1.97 1.11 2.07	calmer, sleeping became more restful started attending a college, tolerates more social life concentration ability improved
	6 months					
40 Female	Latent hyperthyreosis Lyme disease	0.5 2x1	55 52 53 52 52	35.44 29.34 30.94 29.31 29.56	0.94 2.15 1.12 1.61 2.07	Tolerates the hormonal changes due to the thyroid disease much better, the intensity of these significantly decreased Got pregnant but had a miscarriage, the cause of this is proved to be anti- cardiolipin positivity, investigation is going on Calmer, sleeps much better, became more forceful
61 Male	Bell - paretis	0.5 2x1	49 50 49 53 51	24.15 26.04 24.03 30.86 26.75	0.48 0.88 0.29 1.37 1.26	Bell paretis improved significantly, only a slight deviation of the mouth is experienced.
	6 months					
42 Male	Fatty liver Autoimmune hepatitis	0.5 2x1	59 67 55 48	45.4 - 76.86 36.26 22.54	1.34 - 5.22 2.65 3.27	values of laboratory test and general health improved strain using the power increased more restful sleep gained no weight.

## **Changes of symptoms**

Subjective complaints and symptoms of our patients were also investigated. The patients reported general improvement of their symptoms, several patients described significant improvement in several symptoms.

3 patients felt that C-peptid was not beneficial for them, but in the answers of our questionnaire we could see that they are calmer, more balanced, they do not or less frequently catch infections.

Severe anxiety appeared in a patient with autoimmune disease, smoker, while applying C-peptide, therefore the dosage could not be raised.

25 patients felt more energetic.

Sleeping improved in 17 patients.

14 patients became less exhaustible.

In the cases of 12 patients infections were less frequent.

12 participants became more patient.

Speech improved in 11 patients, both in the cases of childhood disorder, and also adult problems.

Joint pain decreased in 11 patients.

Attention span became longer in 9 patients.

In 7 cases headache, migraine decreased.

6 patients feel less often cold since they apply C-peptide.

Motor skills improved, irritability decreased, depression relieved, allergy or asthma got better, skin symptoms and memory improved, each of these in 6 cases.

# Improvement of symptoms

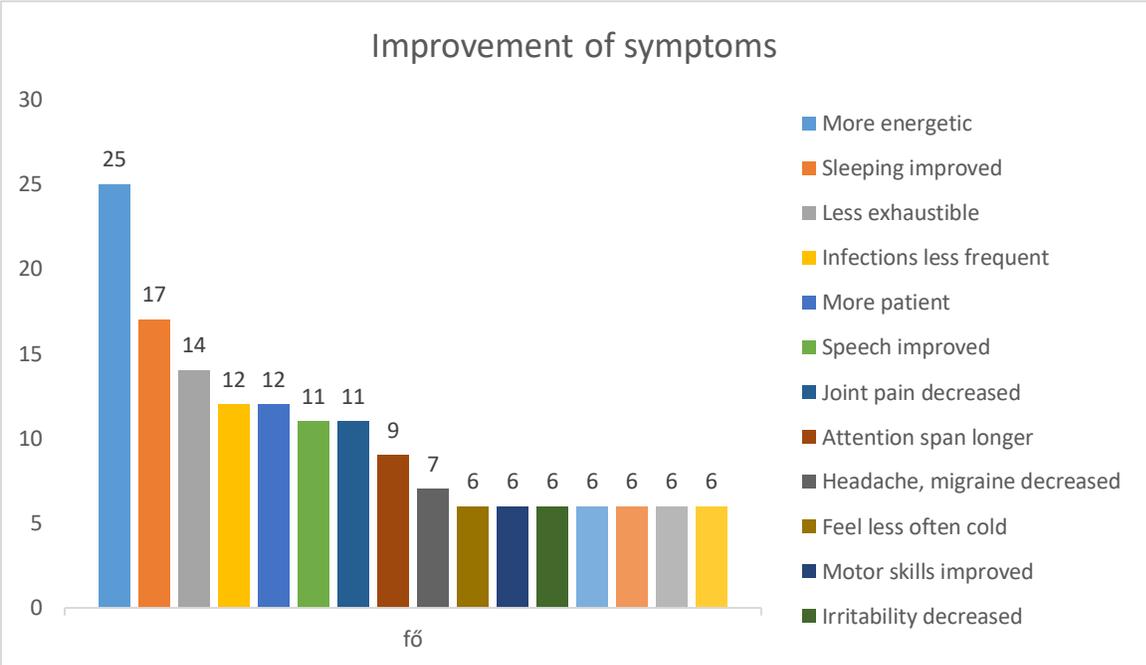


Figure 7 - Improvement of symptoms

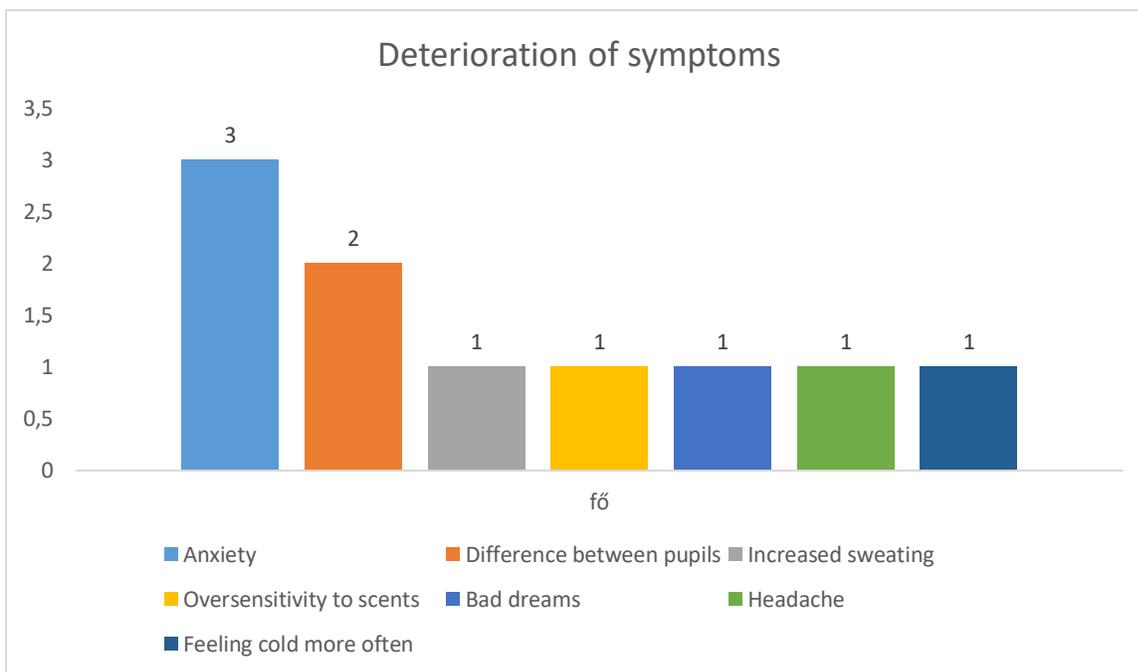
## Deterioration of symptoms

There were rare cases, where the patients reported about deterioration of certain symptoms.

Anxiety increased in 3 patients.

In the cases of 2 patients differences between the pupils appeared.

Increased sweating, oversensitivity to scents, bad dreams, headache and feeling cold more often occurred, each symptom in 1 case.



*Figure 8 - Deterioration of symptoms*

Anxiety, difference between pupils, increased sweating, oversensitivity to scents, bad dreams, headache and feeling cold more often

## **Summary**

Based on our present research it can be stated that the usage of intranasal C-peptide in a longer period (3-6 months) is secure, no serious side-effect or complication occurred during the application. .

Both the objective, measurable values, such as HRV, RMSSD and the LF/HF rate indicated improvement in most cases, and also the subjective complains and symptoms of the patients significantly improved, and due to this their quality of life got better.

The symptoms and the measured values altered according to the dosage of the applied proinsulin C-peptide, therefore the dosage always has to be adjusted to the individual patient.

The patients were cooperating, they want to continue taking C-peptide in the future.

The exact effect, the more precise follow-up of symptoms and narrowing the patient groups in further research studies could provide more accurate image about the impact of intranasal C-peptide.

## Appendix: Spreadsheet of clients

Age Sex	Diagnose	Dosage	HRV	RMSSD	LF/HF	Comments
3 Male	Duchenne	0.5 1x 2x 2-3x	61 68 72 72	53.02 81.16 110.01 106.4	0.73 1,2 7.2 0.57	Face redness milder Immune system strengthened Healing faster when catching a cold Motor abilities improved a lot, sits up independently Lot better adaptation abilities Can walk up stairs Not disturbed by the vacuum cleaner Attention span longer Says more and more words
27 Male	tendonitis, scoliosis	1 1x1 3x0.5 és 2x0,5 1 2x2	61 57 61 59 54 (coke very tired)	51.12 41.37 52.39 45.48 34.5	2.32 2.09 1.88 0.86 1.36	Takes medicine Vegetarian Inflammation flares up less frequently Symptoms improved, than deteriorated again Sweating increased Fatigue got a bit better Attention more focused Forgot to blow C-peptide several times
31 Male	infantile autismus, moderate intellectual disability  6 months	0.5 1x1 2x1 2x1 2x2	71 67 66 57 64	99.33 75.84 74.5 40.77 65.96	0.91 2.1 0.77 4.23 1.42	Sleeping more restful, wakes up at night less often Slightly more skillful in daily activities Hasn't started to speak yet
31 Male	infantile autismus, moderate intellectual disability  6 months	0.5	67 69 73 68 70	78.65 87.33 117.39 81.38 93.22	1.13 2.16 3.24 1.29 1.82	Slightly more skillful Better comprehension and execution of more complex requests
45 Male	Hypertensio n  6 months	0.5 1x11 2x2 1 2x1	58 57 55 68 48	42.75 41.1 35.18 81.12 22.84	5.75 1.67 1.58 2.9 5.89	Takes medicine Knee pain slightly reduced Depression, irritability improved a lot, more balanced and patient at work as well. Concentration improved, more energetic. If he forgets to blow C-peptide, immediately more tired.
67 Female	IBS pain of unknown origin	0.5 1x1 1x2 2x4 2x6	67 41 50 46 59	80.21 14.44 26.25 19.35 47.73	0.51 8.04 1.08 1.42 2.15	Takes several medicine Smokes, stressful Earlier suffered from herpes, during the investigation none Occasional cough stopped

		2x6				Joint pain relieved Depression due to COVID worsened, hard for her to cope with the lock down Takes coffee and smokes before the measurements
	6 months					
45 Male	ragweed allergy	1 1x1 1x1 3x1 4-5x1 8x1	54 55 46 58 56	33.41 35.07 19.31 42.91 37.27	5.36 5.4 8,12 1.99 2.24	No symptom, ragweed allergy milder after 3 months, after 6 months no symptom Joint pain ceased
44 Female	hypo-thyreosis obesity joint pain, hyper-tension	1 1x1 2x2	58 52 49 51 56	44.28 30.2 23.46 28.12 38.34	0.41 4.01 1.13 4.5 1.59	Takes medicine Got COVID infection, than felt unwell due to high blood pressure, rosszul lett Insulin resistance is under examination Memory disturbance appeared After COVID her memory deteriorated, has difficulties to concentrate Feels less fatigue when applying C-peptide Due to COVID the measurement took place was 1 month later
56 Male	Diabetes type 2, joint pain	0.5 1x1 2x1 2x2	66 74 58 48 49	71.37 120.47 43.97 22.25 23.92	0.96 2.19 0.56 1.57 0.65	Takes medicine Did not feel significant change Feels a bit calmer and more balanced Works a lot, exhausted
59 Female	malignant lung and breast tumor	1 2x1 2x2 2x2	52 45 36 (did not take for 4 days during chemotherapy) 52 48	30.3 18.74 10.53 29.26 22.15	1.72 2.37 4.91 0.98 2.32	takes several medicine, receives chemotherapy smokes After 6 months chemotherapy check-up arm itching remained, numb toes, surgery after the 2. test she is in healing phase, feels well, joint pain ceased general health better, but feels weak due to chemotherapy and radiation therapy
78 Female	Skin- and breast cancer, spinal hernia CMP	0.5 1x	54 47 53 61	33.05 21.05 30.53 51.05	1.04 2.25 3.41 0.58	Takes medicine Did not perceive changes (negative thinking is typical, „glad to be alive”)
13 Male	Dysgrafia Attention	0.5 1x	57 60	40.07 49.37	1.68 3.02	earlier severe depression, fear, fear of death

	deficit Behavioural disturbance	after 6 months 1	60 57 57	48.12 41.71 40.21	2.58 4.8 2.94	Already after 3 months symptoms of depression rare, fear ceased Emotional stress, symptoms of adolescence Attention span longer, after 3 months concentration improved, better at school Attention deficit milder after 3 months, fatigue appears less frequently, more restful sleep at night
3 Female	Sensory integration disorder, attention deficit	0.5 1x 0.25 2- 3x 0.5 3x	65 60 79 65	66.7 50.31 172.53 67.85	0.94 0.62 0.28 0.81	After 3 months toilet trained Does not wake up at night, earlier did several times Has bad dreams, but less frequently Feeling of fear has changed Earlier took metallic things into her mouth, this stopped Much less aggressive, almost none at home Attention better Speech developed a lot, more clear articulation, can say whole sentences Eye-contact more stable
75 Female	hyper- tension, hypo- thyreosis	1 1x1 4x1 8x1 0.5 8x1	60 76 69 60 66	48.3 139.06 87.41 48.35 74.5	0.48 1.92 1.2 0.59 2.33	Feels well, occasional pain unchanged, Wart on her neck smaller, Sleeping better already after the 3. month Tired Earlier had headache, ceased
64 Female	Colitis ulcerosa reflux	1 2x2 3x2 2x2	47 53 53 49 stress ful smok ed 63 stress ful	21.52 30.69 30.73 23.46 58.51	6.15 1.21 3.17 1.13 1.17	Smokes (less, earlier 1 now half packet,) minor waist pain ceased colitis ulcerosa 1x recurred, had bloody stool for 1 day, (CU since 1977) earlier these episodes lasted for 2-3 weeks if the C-peptide dosage was raised, got mild headache learns easier (e.g. dance choreography) short-term memory improved a bit does not catch infections
60 Female	autoimmune thyroid disease	0.5 1x 2x1 0.5 2x2 1 2x2	60 49 ate sweets 51 52 ate choco late,	50.56 23.46 26.97 129.63	4.79 1.13 0.45 0.54	Smokes 15-16 cigarettes daily, her pulse rises, this did not change  Decreased the dosage of C-peptide because of severe anxiety  After initial improvement a stressy period amplified her symptoms  Very stressful, because her husband got

	3 months		stress ful			into hospital
56 Male	prostate cancer  6 months	1 1x1 2x1 0.5 2x2 2x4 2x4	46 53 43 Aspiri n prote ct Alfeti m uno 48 55	20.25 32.25 16.25 22.18 35.67	3.23 0.9 3.5 4.39 1.25	Takes medicine Prostate cancer, bone metastasis (started earlier, decompression surgery) less fatigable (fatigable after chemotherapy) occasional headache, but disappears by itself feels well, last examination indicates slight progression
20 Male	speech disorder, depression  3 months	0.5 1x1	42 27 51 40	14.97 5.87 27.09 13.17	3.51 7.69 1.43 4.94	takes medicine less depressed, feels well, can cope with difficult situations calm, improved a lot, feeling fear deteriorated body temperature changed from low to normal nightmares from 5 weekly to 1 weekly wake-ups at night did not change headaches less frequent pupils a bit bigger
49 Female	deep vein thrombosis, gynecologica l tumor, hyper- tension, sleeping disorder, EBV,  3 months	0.5 1x	37 51 62 61	11.43 27.71 56.01 53.23	2.18 1.33 0.22 1.54	Takes medicine Immune system improved a lot, no eczema Coughs much less, at night not at all Moves more easily, does not lose balance Pain released, but still exists Mood a bit better, but has a lot of emotional stress Grinds her throat much less frequently, no dysphonic tone Much more forceful, memory improved, Jaw clicks milder, facial numbness got better Symptoms relieved (confinement) less sensitive to light and sounds
41 Female	pollen- and peanut allergy varicose vein neurastheni a  6 months	0.5	57 59 57 55 59	41.08 46.56 40.19 35.37 46.18	2.65 2.27 3.32 1.9 2.09	feeling heavy foot ceased memory improved got COVID infection before the 3. months measurement
60	tachycardia	0.5	68	83.54	0.26	takes medicine

Female		1x1 2x2 2x2 1 2x2	47 50 51 42	20.68 25.05 26.91 15.39	1.13 0.97 0.99 2.54	earlier frequent herpes did not recurrence during the investigation ear peeling, itching ceased after 3 months more forceful, feels improvement in everything
70 Female	facial neuralgia, COPD, vaso-constriction, osteoporosis, dementia, depression	0.5 1x 2x1 2x2 2x2	43 59 64 46 ate chocolate, 43,	16.24 46.84 62.29 19.82 16.39	1.52 6.61 1.36 1.4 0.73	takes several medicine smokes reflux got better after 3 months had fracture after 3 months, recovered feels more often cold does not really feel improvement depressed mood, upset
43 Female	hypertension left side ovarian cyst, hearing loss (80%),	1	52 57 56 50 69	29.93 41.97 38.94 26.13 91.95	2.68 0.48 6.74 3.24 0.56	eczema ceased symptoms of pollen allergy did not appear had a mild heart attack due to emotional stress - catheterization pain in limbs ceased after 3 months very stressy due to work more forceful, but after the heart attack fatigable again regular headache released, ceased after 3 months attention skill better, memory improved but than deteriorated after the heart attack after 3 months felt definitely better, but after the heart attack it's not the same
53 Female	metabolic disorder, small intestinal bacterial overgrowth (SIBO) menopause food allergy	0.5 1x 2x 2x 2x	66 48 60 72 59	74.79 22.15 47.83 106.02 45.47	1.23 0.88 1.5 0.38 4.97	earlier frequent herpes did not recurrence during the investigation frequent headaches became less frequent waist pain ceased after 3 months, but than recurrence due to constant sitting chole problem, vomits during migraine ceased more balanced, feels cold less frequently more forceful after 3 months, forceful after 6 months handwriting improved concentration ability better hard to cope with menopause, craving for sweets is worse
52 Female	Sclerosis multiplex	1 2x1 2x2 2x1	46 50 50 56	19.7 25.43 25.68 39.08	4.57 3.62 1.78 1.66	does not feel significant change does not catch infections constipation partly relieved before measurement coffee, cake, chocolate

33 Female	IBS anxiety  6 months	1 1x 2x 4x 2x	60 65 66 73 76	49.05 70.56 74.79 118.44 137.23	2,57 1.06 1.41 1.16 1.74	after 3 months diarrhea ceased (no stool at the week-end) better in standing up for herself jobban ki tud állni magáért headache less frequent
46 Female	breast cancer, bones and brain metastasis  6 months	0.5 1-es	56 61 63 58 52	37.45 53.45 61.52 44.16 28.74	2.09 0.58 1.14 2.38 2.19	medications, chemotherapy mood swings, became oversensitive to odor
70 Male	brain injury stroke hyper- tension  3 months	0.5 2x2	69 51 74 69	89.4 27.22 126.01 89.46	1.56 2.57 5.02 0.76	takes several medicine skin improved after 3 months feels cold less frequently, limbs less cold sleeps more restfully concentration, memory did not improve speech improved, comprehension did not less clumsy
51 Female	end-stage renal failure, hyper- tension malignant skin tumor, panic disorder  6 months	0.5 1x1 2x1	70 67 86 - 59	92.16 77.87 260.17 - 46.85	0.14 0.16 8.9 - 0.46	takes a lot of medicine, she is under dialysis treatment ear clicking ceased, occasional headache had knee swelling and pain, pain stopped, swelling remained feels cold less frequently anxiety, panic did not improve, urine returned in 4-5 weeks, but her condition deteriorated after a cystitis 3 months check-up missed due to COVID
59 Male	stroke   6 months	dosage unclear	42 49 78 68 65	15.15 24.37 161.4 101.74 68.63	1.00 2.49 2.3 3.51 1.02	takes medicine had herpes zoster, ceased pain due to duodenal ulcer did not appear feels cold less frequently, sleeps better short term memory, reading improved Feels to have reached 90 % of his capacity before the stroke Felt 80-85% improvement after 1 month Forceful
26 Male	athetosis cerebral paresis spastic tetraplegia perinatal injury	1 1x	77 68 80 77 79	152.38 84.15 181.63 151.56 167.67	2.19 4.3 2.81 3.86 2.21	cold feet symptom decreased sweating released after 3 months significant changes in muscle tone bending better when seated a few words more clear less food falls out when he is eating 6 months: athetotic movements decreased

	6 months					Lines are finer when painting severe sweating released understand longer textes better faster in typing on the computer
46 Female	tinnitus coordination disorder migraine  3 months	0.5 0.5 0.5 0.25	52 69 66 73	29.43 88.25 72.78 118.32	2.52 0.98 2.03 0.93	earlier had herpes, it did not appear during the investigation sleeps better, more forceful attention a bit more concentrated tinnitus did not change after 1-2 months dosage decreased to 1,25 because of bad dreams and fears
34 Male	Asperger          6 months	0.5 1x 0.25 1x 1x 1x	58 40 55 46 52	44.39 13.89 35.73 20.54 30.15	3.58 4.45 4.2 4.47 1.94	takes medicine sleeps more restfully, less fatigue energetic (6 months) concentration improved a lot bipolar depression improved than it's changing headache released than fluctuating, not so sensitive to bright lights does a physician found one of his pupils smaller his opinion is that C-peptide is not useful therefore often misses usage feels stressy when applying therefore dosage is decreased anxiety increased
18 Female	autismus pervasive developmen tal disorder myoclonic epilepsy	0,5 5x 1-es 2x1 2x2 2x3	74 77 63 65 58	122.84 148.86 61.06 67.53 43.84	0.85 1.18 1.33 0.52 1.59	takes medicine for epilepsy sleeps better muscle twitching seemed to be improved after 3 months, but it became fluctuating again no myoclonic epilepsy a physician found one of his pupils smaller says surprising new things, that was not typical before after 6 months után sometimes communicates surprisingly well, speaks as an adult, draws consequences, rounds
24 Female	stroke hypothyreos is	1 2x	66 59 62 51	73.91 45.82 55.37 26.74	1.00 1.14 2.19 2.16	takes medicine QUITTED – since her facial paralysis did not improve asthma improved feels continuous improvement insensitive facial half moves better
26 Male	Asperger food allergy, balance disorder, dizziness,	0.5 2x	56 65 62 54 54	37.96 66.91 56.28 33.46 34.08	2.97 0.76 8.21 3.67 4.76	symptoms of eczema decreased reaction to sweets: spinning, wandering stereotypic behaviour milder balance disorder improved dizziness decreased

	EBV					3 months: 6times/day, 10/5 grade after 6 months:1-2/week, 10/2 grade can sit still, study for 10-12 hours, earlier walked around pupil dilation ceased speech more clear social communication improved a lot more independent, goes shopping independently stress tolerance improved
53 Female	anxiety, waist pain	1 1x1	65 49	68.88 24.27	1.4 4.86	cigarettes 1 packet /day 5 months check-up
58 Female	stress, constant fatigue	1 1x1	55 62	36.78 55.6	1.88 1.58	4 months
24 Female	autoimmune	0.5 1x 0.5 2x	71 73	98.41 117.97	0.51 0.75	4 months
27 Male	Angelmann syndrome	1 1x1	75 71 67	133.49 101.61 79.17	- 0.34 0.56	sleeps better, behaviour more balanced aggressive behaviour decreased willingness to communicate increased did not start speaking 3 months – 5 months
70 Male	2 stroke pacemaker	1 1-1	71 54 81	103.22 33.89 190.39	0.7 1.48 1.04	takes medicine speech improved 3-6 months
67 Female	torticollis	1 1-1	25 63 66	29.77 61.27 73.92	0.69 1.34 0.14	took pain killer, that she did not need any more vitality, exhilaration increased first fatigue released after 1 week, than the pain after 3 months 3-5 months
50 Female	autoimmune , reflux	1x2	36 44 40	10.59 17.61 13.78	6.66 1.38 1.88	vitality, activity improving 3-5 months 5 months: hasn't used for 2 weeks
59 Female	stiatica, palvic tumor	1 2x2	56 44	37.83 17.24	3.08 4.34	takes several medicine, recovered from COVID within 5 days  chemotherapy, radiation treatment  vitality improved, high pulse Due to covid changed for immunotherapy after 3 months
66 Female	hyper- tension 4 months	1 1x1	49 53	24.2 31.06	2.53 2.06	4 months decreased dosage of medication
72 Male	dementia tumor - radiation therapy,	1 1x1	61 68	52.93 85.83	3.22 3.11	speech ability fluctuating, more cheerful, more energetic

	surgeries					
	3 months					
60 Female	bilateral earache dizziness, nervous exhaustion	1 1x1	61 66 76	52.28 71.47 141.07	0.22 1.11 1.65	dizziness ceased earache persisted  4-6 months
	6 months					
56 Female	autoimmune Hashimoto 2 atrophic thyroid lobe	0.5 1x 1 2x2	39 49 55	12.64 12.83 36.56	3.02 1.43 1.14	1 week 6 months no other data
	6 months					
54 Female	hyperthyreo sis  irritable, low stress tolerance, fatigue for 5 years, spinal hernia frequent migraine	1 2x	92 90	22.53 22.01 (erős stressz)	2.86 2.14	takes medicine forceful, cheerful, energetic sleeps well migraine ceased  3 months
	3 months					
24 Female	abdominal pain of unknown origin, vaginitis nephritis, frequent migraine reflux	1 2x	59 60	46.98 50.12	2.01 1.09 (nagyo n beteg felfázás )	headache ceased other problems persisted caught a cold several times, inflammation fluctuated  received antibiotics 3 months
	3 months					
44 Female	autoimmune disease	0.5 2x2 2x2-3	47 47 54	20.79 21.56 33.10	1.29 6.53 2.64	energetic cheerful sleeps well
	2-4 months					
28 Female	pregnant nausea weakness	0.5 1-1	55 57	35.34 3.72 (?)	1.75 1.86	initial measurement at 4. months of pregnancy, after 1 month of C-peptide application in the 9. month: worried because the amniotic fluid is too little
27 Male	sclerosis tuberosa	1 1x1	52 45	29.17 18.43	0.88 1.46	more communicative can manage timing of sleeping periods

	1 months		60	49.9	1.00	1 week 1 month
44 Female	fatty liver high liver enzyme  3 hónap	0.5 2x1 2x2 1 2x1	69 72 68 62 60	91.49 110.87 82 56.34 50.58	5.83 1.81 3.97 2.91 1.41	a bit more forceful does not feel a big change 0-1week - 1 month - 3 months
58 Female	Arthritis rheumatica, thyreoid  6 months	1 2x2	42 54 55	15.05 34.42 35.55	1.56 0.9 1.47	Takes medicine, forceful, sleeps well, has great vitality 0.- 3 months- 6 months
66 Female	tumor lymph node swelling at the collarbone	1 1-1	51 44 47 49	26.84 17.43 21.69 23.96	1.03 1.6 0.75 2.03	swelling shrunk 0.-1-3-5 month used 1.5 month before the initial measurement, thank stopped using it.
76 Female	Parkinson's disease  6 months		36 51 52 58	10.46 28.04 29.24 44.22	1.95 0.88 0.7 0.89	Takes medicine Feels much better More forceful
77 Female	extreme hyper- tension arrhythmia  6 months	0.5 1 x	76 79 78	143.25 169.37 161.09	0.43 0.78 0.93	Takes a lot of medicine Feels very well, full of energy Could decrease the dosage of some medication
24 Male	none  0-3-5 months	0.5 2x2	63 73 59	60.95 114.3 46.02	1.47 0.56 3.64	did not apply 2 weeks before the last measurement did not feel any special
11 Male	none  0-3-5 months	1 2x1	64 71 65	64.47 100.49 69.24	0.8 1.59 2.05	
43 Male	anxiety, skin problems  6 months	1 2x 2-3x	62 58 62	55.81 43.48 57.93	6.35 6.39 3.68	feels much better, not so anxious
29 Male	skin allergy, asthma, migraine	0.5 3-3 2-2	49 72 65	23.94 110.61 70.47	2.04 4.49 4.05	asthmatic and allergic symptoms revealed significantly
62 Female	Leiden mutation right side deep vein thrombosis  0-3-5 months		55 60 73	35.24 49.35 111.52	0.48 1.38 0.54	takes a lot of medicine
77	hypertensio	0.5	58	44.29	0.82	doesn't want to raise the dosage of C-

Female	n	1-1	61 56 63	51.78 36.91 60.56	1.17 0.37 0.41	peptide, because does not dare to decrease the dosage of her prescribed medicine
77 Female	3 stroke hyper-tension perforated heart cardiomyopathy leg pain	1 1-1	48 64 76	22.37 64.98 143.37	0.98 0.92 5.67	takes a lot of medicine forceful, cheerful leg pain ceased due to local treatment
9 Male	COVID last measurement performed right after COVID	0.5 1-1	78 72 75 75	160.17 107.41 134.82 134.75	1.57 1.09 0.45 1.28	forceful, sleeps always superficially  no change  38 degrees at night
55 Male	colon tumor, has already applied C-peptide	1 2-2	63 49	58.86 24.65	3.23 2.85	after colon surgery due to tumor, chemotherapy
56 Female	fatty liver, mild hypertension	1 R3 E2 R4 E2	40 44 51	13.11 17.94 27.01	2.68 1.54 1.74	
47 Female	juvenile Parkinson's disease	0.5 1 2	28 41 49 43 41	6.05 14.48 23.87 16.68 14.2	3.13 4.14 0.82 2.25 8.11	Takes Madopar in every 3 hour, highly fluctuating difficult for her to adjust it to the medication had to decrease dosage to 0.25 did not apply it for 2 weeks before the 4 months measurement
52 Female	pollen-allergy suffered from COVID	1 4x2	- 65 66 78	- 67.83 75.18 157.95	- 1.01 1.8 2.57	
23 Female	Leiden mutation	0.5 1-1	50 77	26.64 147.85	0.6 1.23	Better mood, forceful In case of leaving it out for 1-2 days, a lot more exhaustible, bad mood
64 Female	colon tumor, chemotherapy		53 46	32.33 19.4	53 46	chemotherapy, medicine fluctuating health condition

	py 0-3-5 months		49	24.2	49	feels herself a lot more forceful
53 Female	Diabetes type 2, Mixed Connective Tissue Disease (MTSD)  0-3-6 months	1 2x	32 52 52 47	8.22 29.38 69.44 21.09	1.92 1.29 0.28 0.59	Takes a lot of medicine Foot swelling, skin problem and fatigue ceased than reoccured because of stress, emotional problems
75 Male	Chronic renal failure Hyper- tension Occlusion Arterial stenosis, Tinitis, Lumbal intervert. disc. disorder	1 1x1 0.5 2x2	61 79	53.13 167.53	0.83 1.1	physical capacity improved sleeping got a bit better  hyper the patient died, therefore the 3 months measurements can not be reported
58 Female	Hypertensio n   6 months	0.5 2x2	51 49 56 50 60	27.99 24.83 38.94 26.11 48.69	2.62 3.93 2.28 2.26 4.18	blood pressure stabilized in the normal range mood and sleeping improved copes with stressy situations better feels more forceful strain using the power improved a lot
20 Male	Infantile autismus  6 months	0.5 2x1	63 68 58 47 49	60.55 82.9 43.54 22.49 24.51	1.65 1.29 1.97 1.11 2.07	calmer, sleeping became more restful started attending a college, tolerates more social life concentration ability improved
40 Female	Latent hyperthyreo sis Lyme disease	0.5 2x1	55 52 53 52 52	35.44 29.34 30.94 29.31 29.56	0.94 2.15 1.12 1.61 2.07	Tolerates the hormonal changes due to the thyroid disease much better, the intensity of these significantly decreased Got pregnant but had a miscarriage, the cause of this is proved to be anti- cardiolipin positivity, investigation is going on Calmer, sleeps much better, became more forceful
58 Female	Psoriasis Rhinitis	0.5 2x1	40 43	13.09 16.7	4.77 7.81	Number and thickness of psoriasis plaques, hyperaemia significantly

	allergica		55 53 49	36.61 30.86 24.38	0.98 1.37 5.78	decreased, in certain places ceased. Runny and clogged nose, eyes tearing ceased after 1 week of application, stopped taking antihistamine pills
66 Male	Stroke hyper- tension	1 2x2				Had only one measurement due to COVID infection
52 Female	Mitochondri al disease, facial numbness	1	49 52 57 61 54	24.01 29.99 41.39 53.21 33.27	1.36 1.77 1.1 1.43 0.71	Visual field results better at eye examination Facial numbness decreased Physical capacity, energy got better
24 Female	Lyme- disease, conversion disorder	0.5 2x1	47 58 52 57	21.28 44.26 29.35 39.98	1.7 1.57 3.57 1.93	According to her narrative she did not feel improvement while applying C-peptide, QUITTED the programme
61 Male	Bell - paresis	0.5 2x1	49 50 49 53 51	24.15 26.04 24.03 30.86 26.75	0.48 0.88 0.29 1.37 1.26	Bell paresis improved significantly, only a slight deviation of the mouth is experienced .
42 Male	Fatty liver Autoimmun e hepatitis	0.5 2x1	59 67 55 48	45.4 - 76.86 36.26 22.54	1.34 - 5.22 2.65 3.27	values of laboratory test and general health improved strain using the power increased more restful sleep gained no weight.
5 Female	ADHD immune deficiency	0.5 1x1	67 65 57 58 65	79.28 68.3 41.87 42.12 66.63	0.63 1.26 1.23 1.5 1.26	Immune status significantly improved, infections less frequent, duration shorter. The characteristic features of ADHD – almost completely resolved. Positive changes proved by an Assessment Committee Integrated into a class Attention more focused, understands tasks, executes assignments.
73 Male	Conn syndrome		59 50 54 49	46.34 25.7 33.81 24.34 22.86	0.58 1.87 1.86 0.54 0.24	Earlier constant arrhythmia became less frequent. RR values are balanced, very rarely low blood-pressure. Stamina improved a lot, can afford much more. When Herpes labialis appeared, C- peptide applied on the skin, blisters ceased in 1 day. Got COVID infection during the investigation, hospitalized for 11 days, unconscious for 3 days. During transportation right arm was bruised, haematoma appeared. Recovered in 1 day, after blowing C-

	6 months					peptide on the skin. Applying VargaPeptide 2, health condition improved, after returning home her weakness and fatigue gradually decreased, works in the garden, takes care of himself, walks a lot, a few km-s.
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## **References**

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- <sup>i</sup> Gidron Y, Deschepper R, De Couck M, Thayer JF, Velkeniers B. The Vagus Nerve Can Predict and Possibly Modulate Non-Communicable Chronic Diseases: Introducing a Neuroimmunological Paradigm to Public Health. *J Clin Med*. 2018;7(10):371. Published 2018 Oct 19. doi:10.3390/jcm7100371
- <sup>ii</sup> Williams DP, Koenig J, Carnevali L, Sgoifo A, Jarczok MN, Sternberg EM, Thayer JF. Heart rate variability and inflammation: A meta-analysis of human studies. *Brain Behav Immun*. 2019 Aug;80:219-226. doi: 10.1016/j.bbi.2019.03.009. Epub 2019 Mar 11. PMID: 30872091.
- <sup>iii</sup> Jarczok MN, Koenig J, Thayer JF. Lower values of a novel index of Vagal-Neuroimmunomodulation are associated to higher all-cause mortality in two large general population samples with 18 year follow up. *Sci Rep*. 2021 Jan 28;11(1):2554. doi: 10.1038/s41598-021-82168-6. PMID: 33510335; PMCID: PMC7844270.
- <sup>iv</sup> Rangon CM, Krantic S, Moysè E, Fougère B. The Vagal Autonomic Pathway of COVID-19 at the Crossroad of Alzheimer's Disease and Aging: A Review of Knowledge. *J Alzheimers Dis Rep*. 2020 Dec 28;4(1):537-551. doi: 10.3233/ADR-200273. PMID: 33532701; PMCID: PMC7835993.
- <sup>v</sup> Jarczok MN, Koenig J, Wittling A, Fischer JE, Thayer JF. First Evaluation of an Index of Low Vagally-Mediated Heart Rate Variability as a Marker of Health Risks in Human Adults: Proof of Concept. *J Clin Med*. 2019 Nov 11;8(11):1940. doi: 10.3390/jcm8111940. PMID: 31717972; PMCID: PMC6912519.
- <sup>vi</sup> Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability among youth with type 1 diabetes: the SEARCH CVD study. *Diabetes Care*. 2013;36(1):157-162. doi:10.2337/dc12-0463
- <sup>vii</sup> Rickels MR, Evans-Molina C, Bahnson HT, Ylescupidez A, Nadeau KJ, Hao W, Clements MA, Sherr JL, Pratley RE, Hannon TS, Shah VN, Miller KM, Greenbaum CJ; T1D Exchange  $\beta$ -Cell Function Study Group. High residual C-peptide likely contributes to glycemic control in type 1 diabetes. *J Clin Invest*. 2020 Apr 1;130(4):1850-1862. doi: 10.1172/JCI134057. PMID: 31895699; PMCID: PMC7108933.
- <sup>viii</sup> Gubitosi-Klug RA, Braffett BH, Hitt S, Arends V, Uschner D, Jones K, Diminick L, Karger AB, Paterson AD, Roshandel D, Marcovina S, Lachin JM, Steffes M, Palmer JP; DCCT/EDIC Research Group. Residual  $\beta$  cell function in long-term type 1 diabetes associates with reduced incidence of hypoglycemia. *J Clin Invest*. 2021 Feb 1;131(3):e143011. doi: 10.1172/JCI143011. PMID: 33529168; PMCID: PMC7843223.

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<sup>ix</sup> Lam A, Dayan C, Herold KC. A little help from residual  $\beta$  cells has long-lasting clinical benefits. *J Clin Invest*. 2021 Feb 1;131(3):e143683. doi: 10.1172/JCI143683. PMID: 33529163; PMCID: PMC7843219.

<sup>x</sup> Johansson BL, Borg K, Fernqvist-Forbes E, Odergren T, Remahl S, Wahren J. C-peptide improves autonomic nerve function in IDDM patients. *Diabetologia*. 1996 Jun;39(6):687-95. doi: 10.1007/BF00418540. PMID: 8781764.

<sup>xi</sup> Schwartz MW, Sipols A, Kahn SE, Lattemann DF, Taborsky GJ Jr, Bergman RN, Woods SC, Porte D Jr. Kinetics and specificity of insulin uptake from plasma into cerebrospinal fluid. *Am J Physiol*. 1990 Sep;259(3 Pt 1):E378-83. doi: 10.1152/ajpendo.1990.259.3.E378. PMID: 2205107.

<sup>xii</sup> Okamoto S, Kimura K, Kitamura T, et al. Proinsulin C peptide obviates sympathetically mediated suppression of splenic lymphocyte activity in rats. *Diabetologia*. 2000 Dec;43(12):1512-1517. DOI: 10.1007/s001250051562.

<sup>xiii</sup> Derkach KV, Perminova AA, Buzanakov DM, Shpakov AO. Intranasal Administration of Proinsulin C-Peptide Enhances the Stimulating Effect of Insulin on Insulin System Activity in the Hypothalamus of Diabetic Rats. *Bull Exp Biol Med*. 2019 Jul;167(3):351-355. doi: 10.1007/s10517-019-04525-w. Epub 2019 Jul 26. PMID: 31346872.