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Journal of Bionic Memory **Review article**

Deep brain stimulation in Parkinson's disease: The selection of appropriate patient candidate

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ABSTRACT

Deep brain stimulation surgery, one of the device-assisted treatments for advanced Parkinson's disease, provides a significant improvement in quality of life criteria when applied to the appropriate candidates. Although the subthalamic nucleus is the main neuroanatomical structure for this surgery, other surgical targets include thalamus ventral intermediate (VIM) and globus pallidus internus. Candidates are selected and evaluated by a dedicated team for deep brain stimulation surgery. The deep brain stimulation team consists of a neurosurgeon, a psychiatrist, a neuroradiologist, an anesthesiologist, and a neurologist, who specialize in movement disorder. The patient's motor symptom response to levodopa treatment and other contraindications are reviewed, and the patient is prepared for deep brain stimulation surgery. This article addresses the criteria for the selection of patients with advanced Parkinson's disease, eligible for deep brain stimulation treatment, as well as addressing the appropriate anatomical targets.

Key words: Parkinson's disease (PD), deep brain stimulation (DBS), appropriate candidates, therapy.

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Introduction

In recent years, the device-assisted treatment options are applied for the treatment of patients with advanced Parkinson's disease (PD). The definition of advanced stage patient has recently been discussed and re-defined. Patients with severe dyskinesia or severe *off* periods, patients with at least two hours of *off* time during the day, postural instability during the *off* period, painful dystonia, and severe freezing during the *off* —regardless of the duration of the disease— are eligible for device-assisted treatment [1-5]. However, the most important assessment scale, except for the situations defined, is the restricted daily life activities. Device-assisted treatments include apomorphine pump-continuous infusion, duodopa intestinal infusion, and deep brain stimulation (DBS) [1-5].

Patient selection

The cause of a third of ineffective surgery outcomes in Parkinson's disease is "wrong candidate selection" [6]. In candidate selection, the patient is referred to surgery by taking into account the risk/benefit ratio. Patient-specific findings and surgical risks of patients with Parkinson's disease are evaluated by a team of experts. The deep brain stimulation team consists of a neurosurgeon, a psychiatrist, a neuroradiologist, an anesthesiologist, and a neurologist, who specialize in movement

disorder. In some centers, the team also includes an internal medicine specialist, neurophysiologist, and Parkinson's disease nurse. The ideal patient for deep brain stimulation is a patient with early onset, a good levodopa response, and uncontrollable motor complications. However, some symptoms of patients may have partial or no response to levodopa [7]. The most important factor to be considered in patient selection is the planning of how to control the levodopa unresponsive symptoms after surgery.

For planning, the following questions need to be answered:

1. Is there an age limit?
2. Are there surgical contraindications?
3. Is there a cognitive dysfunction?
4. If there are too many Levodopa-resistant symptoms (dysarthria, dysphasia, postural instability and walking-balance problems), what will be done and how will the patient be followed up after surgery?

Age

Age is an independent variable, but surgery is not recommended for patients over 75 years of age, although there is no age limit. However, the physiological age of the patient is always taken into account more than his/her calendar age. Looking at the studies, we can see that about a quarter of subthalamic nucleus (STN) and globus pallidus internus (GPi) DBS cases are over the age of 70. Considering the risk/benefit ratio, cognitive reserve in older patients is more limited, levodopa-resistant symptoms are more frequent, life expectancy is shorter, and there are more accompanying diseases [8].

Surgical contraindications

Uncontrolled hypertension before surgery increases the risk of intracerebral hematoma 10-fold during surgery [8]. Moreover, uncontrolled heart disease, permanent stroke and active infection increases the surgical risks. Preoperative magnetic resonance (MRI) examinations are used to rule out structural lesions that increase risk, and small vessel disease and Parkinson-plus syndromes that affect utilization and invite behavioral problems after surgery. Magnetic resonance findings are not appropriate in 9% of patients selected in the clinic, and these patients are excluded from surgical treatment. Moreover, patients with severe cortical atrophy also have a high risk of subdural hematoma after surgery. Other factors that the neurologist should check for and pay attention to when preparing the patient for surgery are as follows:

1. Skin infections
2. Use of drugs effective on bleeding
3. Risk of psychosis and confusion during or after surgery
4. Ability to switch from high-dose and multi-drug treatment to a simpler treatment scheme:

For dopamine agonists and rasagiline, ability to reduce the dose weeks ago and simplify treatment.

Advanced stage patients should be informed about the expected benefits, possible risks, and technical issues and usage problems of all treatments.

Cognitive dysfunction

Dementia is the definitive exclusion criterion for the deep brain stimulation treatment. In these patients, executive functions are severely affected. Patients with advanced age and borderline cognitive function experience an increase in frontal and executive function losses, and decrease in verbal fluency, especially after STN DBS. It is known that

these findings are due to the lesion effect, and do not improve by turning off the stimulator or adjusting the voltage. Identifying patients at risk by evaluating cognitive functions with standard tests is of importance for the success of the treatment. After determining the neuropsychological profile of the patient, psychiatry is consulted to evaluate severe depression, suicide attempts or psychotic symptoms independent of medications experienced in the preoperative period, in addition, the family history of severe psychiatric illness is questioned. Some patients are excluded at this stage. Especially in the first year after surgery, the risk of suicide increases in cases of STN DBS due to the rapid discontinuation of dopaminergic drugs [8]. Patients with Parkinson's disease whose history includes suicide attempts and whose disease started at a young age are not suitable candidates for STN DBS.

Levodopa response

The most important criterion affecting treatment success in surgical treatment is the response of the patient's symptoms to levodopa. Especially for STN DBS, the expected motor benefit in the postoperative period is similar to the levodopa response. If the patient's signs of resistance to levodopa are intense and these symptoms are responsible for the main disability, these patients are not suitable for surgical treatment. When evaluating the Levodopa response, the best on periods of the patient are evaluated, and if necessary, an extra dose is given to see the best on periods of the patient. Patients who are active after Levodopa (at least 1 hour) are the best candidates for STN DBS [9].

In the advanced stage Parkinson's disease, the severity and type of dyskinesia are not important when referring the patient to surgical treatment since both STN and GPi DBS treatments control dyskinesia. However, STN DBS requires a slow voltage increase in the early postoperative period, while in GPi DBS, the patient quickly recovers from dyskinesia after surgery.

There is no defined severity of the disease that will change the way patients benefit from surgical treatment. Dramatic improvements can be seen in patients with high motor scores. Disability and personal factors that the patient is exposed to due to Parkinsonian symptoms determine the success of surgical treatment.

The disease duration is not a primary factor in patient selection for surgical treatment. Looking at patients selected for subthalamic nucleus DBS, it seems that the average duration of disease is 7.5 years, and the average duration of motor complications is 3 years. As the duration of the disease increases, the risk of surgical implantation, technical problems (17.2%) and intracranial bleeding (1-2%) increases [8,10]. Therefore, if the patient has impaired quality of life data despite an optimal treatment, the patient can be referred to surgical treatment, provided that the diagnosis of the disease is accurate. Surgical treatment is usually planned after the first five years, except for patients with resistant resting tremor.

Determination of the surgical target and follow-up of the patient in the postoperative period

Thalamus VIM DBS is selected as a target in patients with resting tremor resistant to levodopa and other treatments in Parkinson's disease. Dysarthria and balance problems may occur in patients due to bilateral stimulation. Another group of patients include patients who are not suitable for other targets due to their age and cognitive profiles: In these patients, severe tremor is easily controlled by unilateral

thalamic stimulation. It is ineffective for bradykinesia and rigidity.

Subthalamic nucleus DBS is the most selected practice. It is effective against bradykinesia, rigidity and tremor. Some of the side-effects associated with bilateral stimulation can be overcome by programming. Dyskinesia, paresthesia and dysphonia occur in 19% of patients, but these are reversible. In 41% of patients, it slows down memory, executive functions and mental speed. These patients should be monitored for depression and hypomania. Weight gain and balance problems occur in almost every patient. Its main advantage is that it reduces the dose of dopaminergic drugs [11-5].

Globus pallidus internus DBS is effective in all cardinal findings, but makes a dramatic reduction in dyskinesia. Adverse-effect profile is lower than STN DBS. The dose of dopaminergic drugs does not change in the post-operative period.

In deep brain stimulation surgery, early postoperative complications include intracerebral hemorrhage (2%), ischemic stroke (1%), seizure (0-3%), and postoperative confusion (21%); and, implant site infection (3-8%) is seen in follow-ups [8]. Especially after STN DBS, cognitive decline, impaired frontal executive functions, decreased verbal fluency and impaired working memory are seen [7].

Neuromodulation settings are performed every 1-2 weeks in the first months of the patient's postoperative follow-up. The average optimal setting time varies from patient to patient in the range of 1-3 months. In subsequent follow-ups, the patient is called to the clinic to check the impedance and parameters at intervals of six months.

Conclusion

As one of the device-assisted treatments for advanced Parkinson's disease, DBS provides a significant improvement in quality of life criteria when applied to the appropriate patient. STN is the preferred target, but thalamus VIM and GPi are other surgical targets. The most important criterion determining the patient's response to surgery is the levodopa response of the patient's findings. Especially after STN DBS, the patient's antiparkinsonian drug doses can be reduced, so the patient is also protected against the drug side-effects. After DBS surgery, which is applied to the appropriate patient at the appropriate time with the appropriate neuroanatomic target, the follow-up of patients also requires care and patience.

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Journal of Bionic Memory Original article

Dose responses of the SiO_2 used in radiation sensors in field effect transistor form

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ABSTRACT

Aim: To investigate the structural changes in the SiO_2 (silicon dioxide) layer, which is the sensitive region of the RadFET radiation sensors used in the medical field, and to elaborate the impacts of these modifications on electrical characteristics.

Methods: Dry oxidation method was used to grow the SiO_2 film on n-type Si (100) and SiO_2 MOS capacitors were produced by using DC magnetron sputtering. Irradiation was carried out using a ^{60}Co radioactive source at a dose range of 1 kGy-50 kGy. XRD (X-ray diffraction) results showed that no crystalline structure was formed in the studied dose range.

Results: The results obtained from XPS (X-ray photoelectron spectroscopy) showed that Si-Si oxygen deficient bonds were formed in the post-production structure, resulting in the observation of flat band voltage (V_{fb}) at negative values.

Conclusions: In general, the Si-Si oxygen deficient bond content increased with increasing radiation dose, causing the C-V curve to shift towards larger negative voltage values as desired. The device sensitivity was almost constant after 25 kGy.

Key words: RadFET, NürFET, MOS, structural modifications, radiation dose.

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Introduction

The usability of Metal-Oxide-Semiconductor-Field Effect Transistors (MOSFETs) as radiation sensors was first demonstrated by Holmes-Siedle [1], followed by intense research into the use of these dosimeters in different fields. Optimized for the purpose of improving radiation sensitivity, p-channel MOSFETs (also known as RadFETs) are used to obtain information about space-radiation in spacecraft [2], to determine the radiation damage that may occur in electronic components in centers such as CERN where the experiments with high radiation field are conducted [3], and to detect the possible radioactive leakage in nuclear power plants. The forms of these chips placed in the wristwatch are attached to military personnel and serve as a warning system in case of possible radioactive danger [4]. RadFETs are used in skin dose measurements in radiation chest treatment, treatment planning verification

(for photon and electron) in IMRT, in measurements of input-output doses, skin dose, peripheral dose and tumor dose, in IGRT (Image Controlled Radiotherapy), TBI (All or Half body irradiation), Brachytherapy, Stereotactic radiosurgery/stereotactic radiotherapy (SRC/SRT) [5].

The first domestic production of RadFETs was made at Bolu Abant Izzet Baysal University Nuclear Radiation Detectors Application and Research Center (NRDC), and these dosimeters, in which two sensors were placed in a single chip, were named NürFET. The sensitive region of the commercial RadFETs/NürFETs consists of silicon dioxide (SiO_2). The most important reason of this choice is that SiO_2 has high thermodynamic stability with Si and creates excellent interface quality. On the other hand, studies are being carried out on alternative high-k dielectrics to SiO_2 in order to obtain thinner and more sensitive sensors [6].

The calibration of a NürFET radiation sensor is based on the shift in threshold voltage depending on the applied dose. The initial threshold voltages of p-channel NürFETs are observed at negative voltage values, and with the applied dose, the threshold voltage shifts towards larger negative voltage values since the holes are more trapped in the structure than electrons. The most serious problem with high-k/MOS structures is the poor interface quality, and the +3 oxidation level acting as an electron trap center [7]. In some cases, electrons are trapped more in the oxide layer and/or at the interface than in the holes, resulting in electrical characteristics not shifting in the desired direction [8].

Thermal annealing is a common method applied to the structure to remove some defects in the thin film. However, this causes some defects in the structure to not be permanently repaired, resulting in the formation of neutral electron trap centers [9–11]. In addition, since radiation causes local heating in the structure, it creates structural changes [12]. For these reasons, it is extremely important to determine what kind of changes the radiation dose causes in the structure and to define their effects on electrical characteristics. The aim of this study is to describe the structural changes caused by gamma radiation in the SiO_2/Si structure annealed at room temperature (RT) and to detail the effects on the radiation response of a SiO_2-MOS capacitor.

Materials and methods

The possible contamination on 6 inch-n type Si (100) wafer was removed by following the RCA procedure. Dry oxidation method was used to deposit the SiO_2 layer. After the Si wafers were placed in the diffusion furnace, oxygen gas with 3 slm flow rate was sent into the system. Film deposition was made for 2 hours 53 minutes at 1000 ^oC and then the samples were placed in a nitrogen cabinet at room temperature. The thickness of the film was measured at 100 nm with Spectroscopic Reflectometer. A part of the 6-inch wafer is reserved for structural analyses, XRD and XPS. The remainder was used for the production of MOS capacitor.

Metal electrodes of SiO_2-MOS capacitors were created with a DC magnetron sputtering system using a 99.9% purity 4-inch Al target. After the pressure of the vacuum chamber of the sputtering system was reduced to $6.0x10^{-4}$ Pa, argon gas with the flow rate of 16 sccm and the pressure of 1.0 Pa was sent into the system to form plasma. While the front contacts were formed, a 1.5 mm diameter mask was placed on the upper side of the film-covered surface of the structure and Al deposition was performed for 55 minutes at 150 W. For the back contact, the

entire matte part of the wafer is covered with Al under the same conditions for 25 min. Production stages were carried out in 10, 100, 1000 clean room laboratories in NRDC.

The SiO_2/Si structures and SiO_2-MOS capacitors were irradiated with ^{60}Co gamma radioactive source (1.3 kGy/h) at 1 kGy, 25 kGy, 50 kGy at the Turkish Atomic Energy Authority.

The crystal properties of the film were evaluated with XRD analyses and the spectra were taken for the diffraction angle range of 10^o-80^o. XPS measurements of the SiO_2/Si were conducted by using Physical Electronics PHI 5000 VersaProbe (Monochromatic Al Kα X-ray source-1486.6 eV). Depth profiles for the surface, mid of the film and oxide/interface were measured with Ar sputtering (1 keV) to determine the atomic concentrations and bonds. The Si 2p and O 1s XPS spectra were corrected with reference to the C 1s peak of 284.8 eV. De-convolution of the spectra was performed with XPSPEAK 4.1 software.

The electrical characteristics of SiO_2 MOS capacitors were measured by HIOKI-LCR meter at two different frequencies (100 kHz and 1 MHz).

Results and Discussion

The XRD spectra of the SiO_2/Si structures irradiated at three different doses are presented in Figure 1. No peaks were observed indicating crystallization before and after irradiation, indicating that the structure is amorphous. It is important that the structure maintains its amorphous property in the studied dose range in terms of exhibiting a stable behavior.

Figure 2 shows typical Si 2p and O 1s XPS spectra obtained from SiO_2/Si structure. No carbon content was found in layers other than the surface. The peak centered at ~98.6 eV in the Si 2p spectrum represents Si-Si bond, while the peak located at ~103.3 eV shows Si-O-Si bond. In the O 1s spectrum, the peak centered at ~532.2 eV is associated with the Si-O-Si bond. Since hydroxyl species adversely affect the electrical characteristics of the sensor, it is desirable that it is not in the structure or observed at a minimum level. No peaks were observed indicating the presence of hydroxyl species in the film.

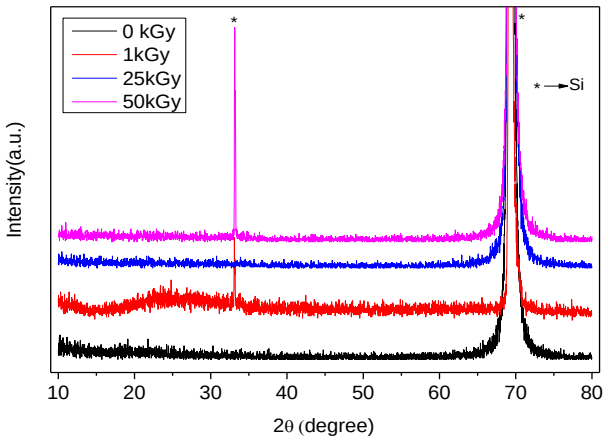

Figure 1. XRD spectra of the SiO_2/Si structures irradiated in the dose range of 0-50 kGy.

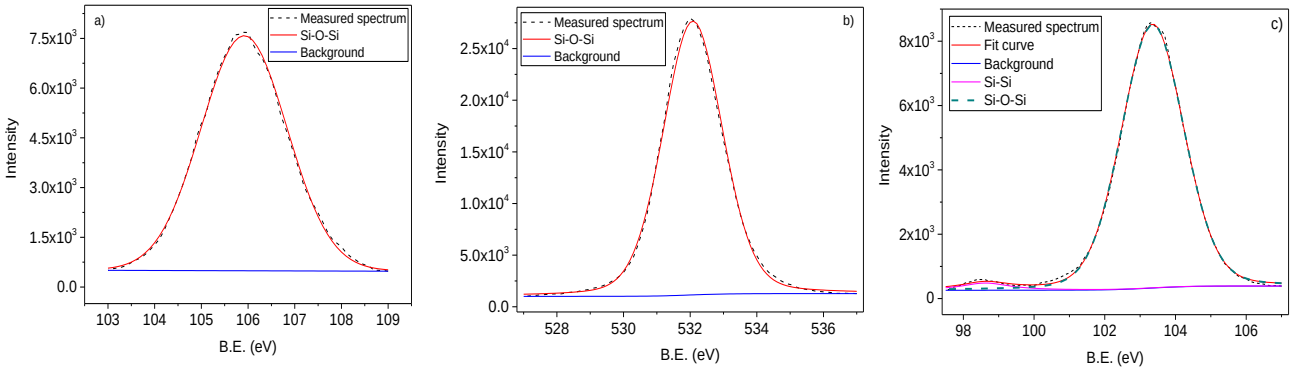

Figure 2. SiO_2/Si XPS spectra: a) Si 2p for film, b) O 1s for film, c) Si 2p for interface.

Depth-dependent variations of atomic concentration (A.C.) values of Si and O in non-irradiated and irradiated SiO_2/Si structures are given in Figure 3.

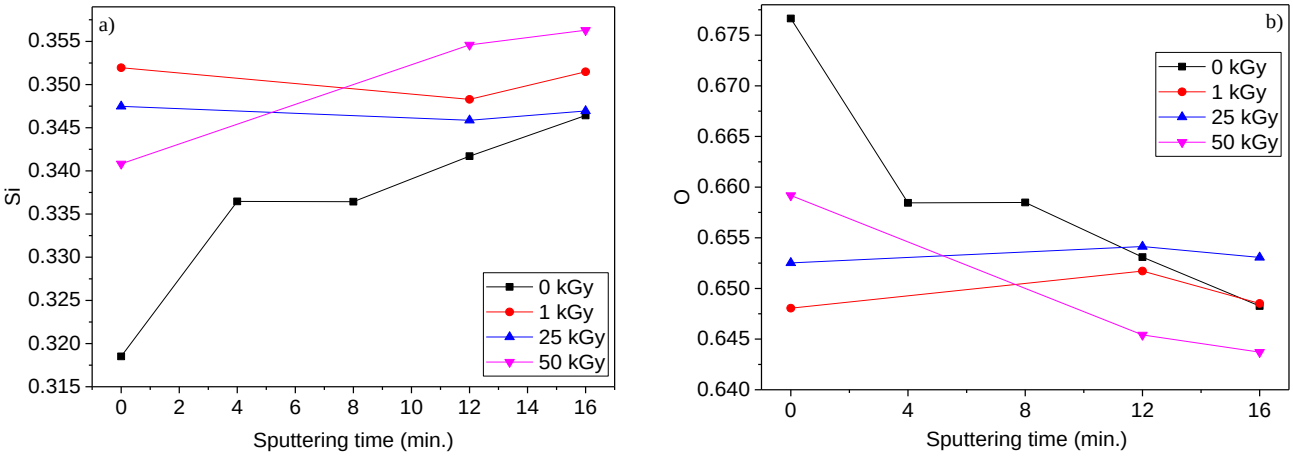

Fig. 3. Depth-dependent Si and O atomic concentrations: a) Si, b) O.

It is theoretically expected that there will be 33.3% Si and 66.7% O in the structure. The results in Figure 3 show that the production meets the theoretical expectation to a great extent. Figure 4 shows the variation of the signal intensity of the Si-O-Si peaks in the O 1s spectra depending on depth of the film.

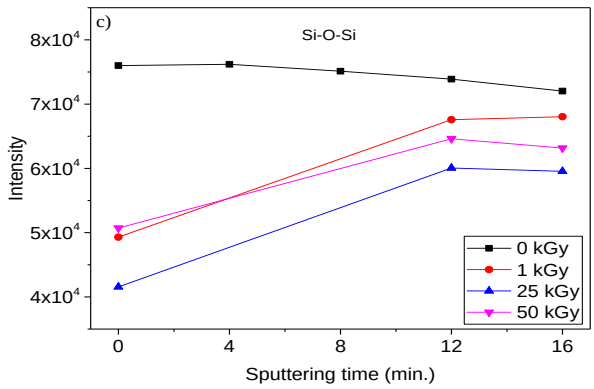

Figure. 4. Intensities of the Si-O-Si peaks in the O 1s spectra.

Post-production Si concentration was generally above 33.3% at all depths as can be seen from Fig. 3. This indicates oxygen deficient Si-Si bonds in the structure that do not participate in bonding with oxygen. However, since the signal intensity is weak, a second peak indicating Si-Si bonds in XPS spectra was found only at interfaces. It has been reported that the Si-Si oxygen deficient bonds act as hole trap centers [13]. For this reason, positive charges are expected to be more dominant than negatives in the post-production structure. Si concentration increased with the irradiation of 1 kGy in the film and oxygen content decreased. Although the Si concentration is high at 1 kGy compared to 0 kGy, the oxygen concentration is similar to the values obtained from the non-irradiated sample. On the other hand, the Si-O signal intensity is also lower than the values obtained from the non-irradiated sample. These results indicate an increased concentration of defects acting as positive charge trap centers both in the oxide layer and at the interface. Therefore, the C-V curve is expected to shift to the left with 1 kGy irradiation, compared to the pre-irradiation electrical characteristic. The Si concentration in the film and at the interface is generally high at 25 kGy compared to the values obtained from the non-irradiated structure, and lower than the values obtained at 1 kGy. The oxygen concentration at 25 kGy tends to be higher than values obtained from irradiated at 1 kGy and non-irradiated structures. When the irradiated structure at 25 kGy is compared with the non-

irradiated structure, it is seen that although the Si concentration at the interface is at a similar level, the oxygen concentration is higher at 25 kGy, resulting in a less positive charge defect center content at the interface at 25 kGy. On the other hand, the difference between Si concentrations in the film is higher than the difference between oxygen concentrations. This means that the positive charge trap center concentration in the film at 25 kGy is higher than in the non-irradiated structure. Therefore, the electrical characteristics are expected to be more left compared to those obtained from the non-irradiated structure after 25 kGy irradiation. When the results of 25 kGy and 1 kGy are compared in terms of atomic concentrations, it is expected that the positive charge trap center content in the structure at 25 kGy is less. However, as can be seen from Figure 4, Si-O content is lower at 25 kGy. The absence of oxygen in the Si-O-Si bond may have caused an increase in the Si-Si content in the structure. Therefore, it can be said that positive charge traps are higher at 25 kGy compared to 1 kGy. The Si concentration was found to be the highest and the oxygen concentration the lowest at all depths except the surface at 50 kGy. Although Si-O-Si ratio is higher compared to 25 kGy, differences in atomic concentration may have caused an increase in positive charge traps at 50 kGy.

The series resistance is very effective on the electrical characteristics of the MOS capacitor. Therefore, the series resistance correction, which is explained in detail in the Ref. [14], is applied to the data. The corrected C-V characteristics for 100 kHz and 1 MHz of the SiO_2 MOS capacitor taken between -25 V – 15 V before and after irradiation were given in Figure 5.

The dielectric constant of the non-irradiated SiO_2 was calculated as 4.70 using the well-known formula, $C = \varepsilon\varepsilon_o A/d$. The dielectric constant of SiO_2 is 3.9. The reason of the higher value found in this study is that interface trap charges contribute to the measured capacitance [15]. Interface trap charge density (N_{it}) was calculated using Eq. 1 [16]:

$$N_{it} = \frac{2}{qA}\frac{G_{max}/\omega}{\left(\frac{G_{max}}{\omega C_{ox}}\right)^2 + \left(1 - \frac{C_m}{C_{ox}}\right)^2} \qquad (1)$$

where G_{max} is the maximum conductance, ω is the angular frequency, C_{ox} is the oxide capacitance, C_m is the capacitance related to maximum conductance, q is the electrical charge and A is the capacitance area. Post-production N_{it} value was obtained as $5.3\text{x}10^{10}$ $eV^{-1}cm^{-2}$. The change in oxide trap charge density (ΔN_{ox}) occurred with the irradiation was calculated in the following expression [17]:

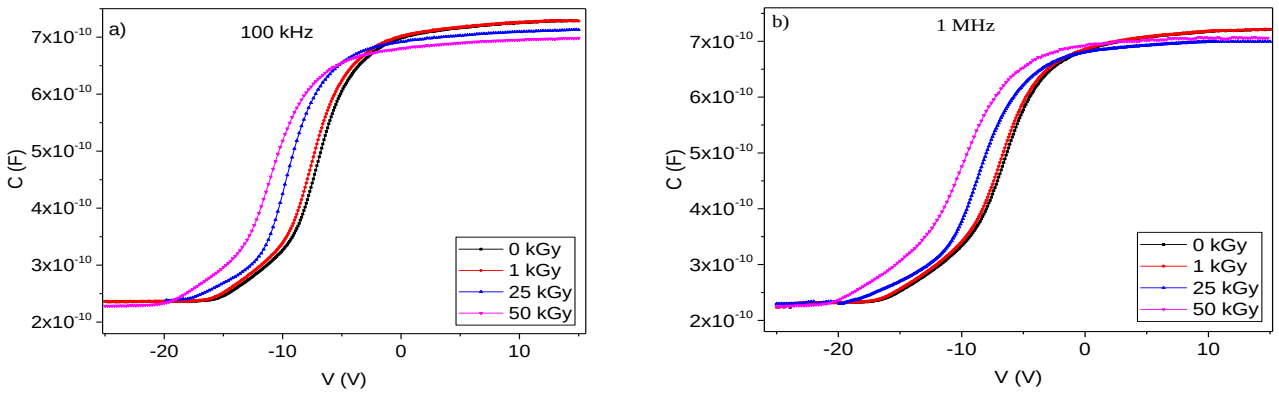

Fig. 5. C-V curves of SiO_2 MOS capacitor before and after irradiation:a) 100 kHz, b) 1 MHz.

$$\Delta N_{ox} = -\frac{C_{ox}\Delta V_{mg}}{qA} \qquad (2)$$

where ΔV_{mg} is the change in mid-gap voltage. The ΔN_{it} (change in the interface trap charge density with dose) and ΔN_{ox} values depending on the dose are given in Figure 6a. No major change in the ΔN_{it} values was observed in both frequencies with increasing dose, indicating that the device performance is not adversely affected in the dose range studied. ΔN_{ox} values increased with increasing dose as expected. Device sensitivity was calculated by dividing V_{fb} by dose and the values are given in Figure 6b. The sensitivity of 25 kGy and beyond is almost similar, indicating that the device has reached saturation.

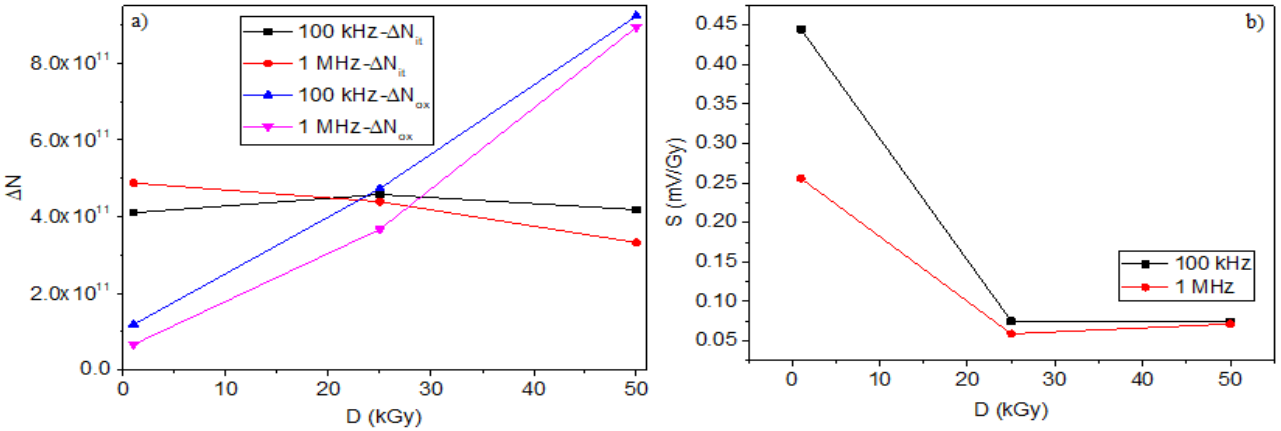

Fig. 6. a) Sensitivity, b) Dose-dependent ΔN_{ox} and ΔN_{it} values of the SiO_2 MOS capacitor.

The radiation response of the MOS capacitor with a 240 nm thick SiO_2 layer for 64 Gy is reported as 4.03 mV/Gy [18]. An increase in the thickness of the sensitive region can improve the sensitivity of the sensor. On the other hand, it is known that the dose response deviates from linearity as higher doses are reached [19,20].

Conclusion

Structural modifications in SiO_2/Si structure that occur after production and with irradiation were investigated by XRD and XPS techniques. In addition, a connection was established between the electrical characteristics and structural analysis of SiO_2 MOS capacitors. SiO_2 film preserved its amorphous character up to 50 kGy. XPS results showed that mainly oxygen deficient Si-Si bonds were formed in the structure with production and irradiation. Si-Si defect content tends to increase with increasing radiation dose. An increase in oxygen concentration does not always indicate less oxygen deficient bond. In addition to the oxygen concentration, the formation of Si-O-Si bond is also effective on electrical characteristics. There is no important change in the N_{it} with the increasing radiation dose, indicating that the performance of the device does not deteriorate up to dose of 50 kGy. The ΔN_{ox} values increased with increasing radiation dose as expected. Since the device was saturated at 25 kGy and beyond, there was no significant change in its sensitivity after this dose. The focus of future studies should be determining the types of traps in devices produced with different dielectrics and improving the sensitivity of the sensor.

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Journal of Bionic Memory **Review article**

Leadless and symbiotic cardiac pacemakers; as an alternative to conventional pacemakers

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ABSTRACT

There have been considerable advancements in technology since the first permanent pacemaker was implanted in 1960. A subcutaneous generator and battery module are connected to one or more endocardial leads in the conventional pacemaker implantation. Despite their proven efficiency, traditional permanent pacemakers have a number of drawbacks their use has been linked to potential complications during implantation procedure and also during follow-up period; among the most notable ones are lead malfunction, limited battery life, and device-related infections. Therefore, there had been tremendous efforts to avoid such complications and to increase battery life. In this Review, we explore new electronic devices, leadless pacemaker systems and symbiotic cardiac pacemakers, designed to avoid these current limitations.

Key words: Heart, cardiac surgical procedures, instrumentation, cardiac pacemaker, leadless, symbiotic.

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Leadless Cardiac Pacemakers

Approximately one million new pacemakers are implanted each year [1]. Complications are seen in approximately 10% of patients during and after the implantation of permanent pacemakers [2,3]. These complications which are primarily lead- or pocket-related, include pneumothorax, tamponade, hematoma, venous obstruction, lead breakage/dislocation, tricuspid regurgitation, and infection [4-6]. Therefore there had been continuing efforts to improve pacemaker technology for easy use and to avoid complications.

To address these issues, Leadless pacemaker (LPM) research was started after the second half of the 20th century. LPM was successfully implanted in the right ventricle for the first time in 2012 [7-9]. Due to its single chamber pacing feature only, it is suitable for use in a limited number of indications. These are (1) Permanent atrial fibrillation (AF) with atrioventricular (AV) block or AF with a slow ventricular response (2) Sinus rhythm with $2^{nd}/3^{rd}$ degree AV block and significant comorbidities or (3) sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiology findings (like prolonged HV interval) [10].

The two LPM systems (Nanostim™ (St. Jude Medical, Inc., St. Paul, MN, USA) and Micra™ transcatheter pacing system (TPS) (Medtronic, Inc., Minneapolis, MN, USA)) that are currently available have demonstrated comparable performance and safety results. Data for both Nanostim and Micra showed an equally high degree of implant success, ranging from 99 to 95%. The overall non-complication rate for the Nanostim was around 94% and for the Micra it was around 96-98.5%. Both LPM

system are similarly implemented with fluoroscopic guidance in the catheterization laboratory. Dedicated introducer sheaths are used which measure 18/21 French for Nanostim LCP and 23/27 French for Micra TPS. Percutaneously a LPM device is introduced through the femoral vein that is mounted on the deflectable tip in the end of the delivery catheter. Then, through the vena cava inferior, to the right atrium and through the tricuspid valve, the deflectable delivery system is moved to the right ventricular myocardium. The device is fixated by either a screw-in helix (Nanostim LCP) or nitinol tines (Micra TPS). The device is discharged from the delivery system following an electrical threshold test and a tug test for stability. The two devices have been designed to be removed after implantation using a snare [11,12].

Due to the fact that the device is leadless, electrode bending and possible damage to the lead are prevented. Device pocket and transvenous lead removal can also minimize some of the long-term pacemaker complications such as tricuspid valve regurgitation and thromboembolism [13]. Leadless pacemaker implantation appears to have a slightly higher acute period complication rate compared to traditional pacemaker (TPM) implantation (4.8% versus 4.0%) [14]. This is probably due to unfamiliarity of operators to new LPM system technology and lack of experience for their implantation.

The results of the Micra study showed that LPM has a 48% lower complication rate, 47% lower yearly hospitalizations and 82% less pacemaker re-insertion rate than TPM [15]. A prospective, multicenter, non-randomized trial with the safety of the LCP Nanostim in a real world was the LEADLESS Observational study. In 95 percent (285 of 300) of the patients, freedom from grave adverse events was observed after 6 months of Nanostim LCP implantation. However, cardiac perforation (1.3%, n=4) and vascular complications (1.3%, n=4) were reported [16]. Sattar et al. searched the complication rates of conventional and leadless pacemakers in a retrospective review published in 2020. They reported that LPMs had better safety profiled with lower electrode dislodgement (56% vs 7%, $p< 0.0001$), pocket site infection (16% vs 3.4%, $p= 0.02$), and lead fracture rate (8% vs 0%, $p= 0.04$). However, LPMs had a statistically non-significant two-times high risk of pericardial effusion (8% vs 4%, $p= 0.8$) [17].

In all, comparable performance and safety results were demonstrated by the 2 LPM systems. Pneumothorax and infection with pocket/lead did not occur as expected. The leadless procedure was however associated with femoral vascular complications unique to percutaneous insertion of the device, intraoperative repositioning and a moderate risk of cardiac perforation that lead to pericardial effusion. Despite many advantages in terms of pacemaker pocket and lead-related complications risk reduction, LPM therapy is currently available only for VVI pacing, which represents <15% of the pacemaker population.

It is difficult to compare complication rates of 2 leadless pacemaker systems exactly, due to several differences in study design. The main difference was the definition used for the primary safety outcome in the studies. If the major complication criteria in the Micra TPS study were used in the Leadless II study, the reported complication rate could decrease from 6.5% to 4.9%. There was a difference in device displacement rate between LCP and TPS (2.3% vs 0%). This indicates that the screw fastening mechanism of the LCP may result in a higher risk of dislocation. Experience is very

important in fixing the LCP correctly. Actually evidence for this was seen in the European LEADLESS Observational Trial. At the beginning of the study, fatal pericardial tamponade was observed in 2 of 147 patients and the study was stopped. After the physician training program, this rate decreased to 0 in 93 patients [14]. In the Micra study, there was no evidence between operator experience and major complications [18]. On the other hand, the researchers showed that patients with older age, female sex, low body mass index, and chronic lung disease are more likely to suffer from cardiac injury [19]. Estimated battery life calculated using actual usage data at 6-month follow-up is 15.0 years for LCP and 12.5 years for TPS [20]. However, different methods have been used to estimate the battery life for 2 devices and have a significant effect on the predicted longevity. LCP, ISO standard 60 beats / minute at 0.4 ms, 100% pacing nominal settings at 2.5 V were used. The TPS used an alternative nominal setting of 100% at 1.5 V at 0.24 ms at 60 beats / min. If the TPS longevity estimate was instead calculated using ISO nominal settings, the battery life would be reduced to 4.7 years [21]. Five major significant publications of these two types of LPM are compared in Table 1.

Table 1. Major clinical trials of cardiac leadless pacemaker treatment.

Study	Number of Patients	Follow up Time	Primary end point	Finding and Notes
LEADLESS (2014)	33	90 days	Freedom from complications	The overall complication-free rate was 94% (31/33). After 3 months of follow-up, the measures of pacing performance either improved or were stable within the accepted range.
LEADLESS II (2015)	526	180 days	Freedom from device-related serious adverse events	Observed in 6.7% of the patients; events included device dislodgement with percutaneous retrieval (in 1.7%), cardiac perforation (in 1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (in 1.3%)
The Micra Transcatheter Pacing Study (2015)	744	183 days	Freedom from major complications related to the Micra system or implant procedure	The percentage of patients free from major complications is significantly higher than 83%, both low and stable thresholds is significantly higher than 80%.
LEADLESS Observational Study (2018)	470	180 days	Evaluation of safety via freedom from serious adverse device effects	The rate of freedom from serious adverse device effects was 94.6%
The Micra Post-Approval Registry (2017)	795	30 days	Assess system- or procedure-related major complications through 30 days post implant.	Major complication rate of 1.51%, (cardiac effusion/perforation (0.13%), device dislodgement (0.13%), and sepsis (0.13%))

Promising results are expected from new studies conducted such as LPM alternative pacing modalities, devices with improved battery longevity, possibilities of devices delivering dual-chamber therapy and cardiac resynchronization therapy to expand clinical applicability and cover most indications. Leadless pacemakers have the potential to supplant conventional lead-based pacemakers for most indications.

Symbiotic Cardiac Pacemakers

Including a fixed lifespan that results in lead and/or generator replacement periodically, implantable cardiac pacemakers are not without limitations, despite technological advances. Consequently, a symbiotic pacemaker is a promising technique for dealing with these challenges.

Living organisms are rich in chemical, thermal and mechanical sources of energy [22-24]. The use of these energy sources may be a viable way of overcoming the battery capacity limit, which restricts implantable devices' long-term durability.

In 1999, Goto et al, tested an automatic power generation system (AGS) for quartz watches that converts kinetic energy into electrical energy as a power source for implantable leadless pacemakers in a dog. AGS produced 13 μJ per heartbeat, thus demonstrating that AGS could provide enough energy for use in a pacemaker [25].

A nanogenerator that can harvest biomechanical energy from cardiac motion and thereby power the implanted pacemaker has been developed by Ouyang et al. in 2019. The researchers developed an implantable pacemaker comprising a power management unit, a pacemaker unit and a novel implantable triboelectric nanogenerator (iTENG), containing two triboelectric layers. The iTENG was placed between the heart and the pericardium of a pig; cardiac motion caused periodic contact and separation of the two triboelectric layers, generating electrical energy, which could be stored in the capacitor of the power management unit. The iTENG-based pacemaker successfully converted sinus arrhythmia to a rhythm of pacing in a pig with sinus arrhythmia inducted through sinus node hypothermia. This new pacemaker is described by the researchers as symbiotic because it transforms biomechanical energy from the beating heart into electricity energy for power of the pacing module [26]. The iTENG provides a promising method to harvest in vivo biomechanical energy, with advantages of wide choice of materials, high outputs, good flexibility, light weight, excellent durability and low cost.

To reach clinical applications, the advancement of minimally invasive procedures like interventional cardiac catheterization, which are commonly used in pacemaker implantation, could provide a suitable solution for symbiotic cardiac pacemaker implantation. The size, flexibility, and operability of the instruments should be viewed as a major concern in order to meet the criteria of minimally invasive surgery.

Conclusion

Clinicians are pursuing perfect systems in pacemakers that comply with the normal physiological transmission, are easy to implant, have the least complications, do not contain too many external structures, and do not need an external battery for energy, and with each discovery they are getting one step closer to this. The treatment of heart conduction system disorders is currently performed with traditional pacemakers and recently with leadless pacemakers that have been put into service for humanity for the last 10 years.

Although randomized clinical trials are not yet available, they are expected to cover most of the pacemaker indications. Probably and hopefully, in addition to single RV pacing modality, they will be used for multi-component, dual-chamber pacing and cardiac resynchronization therapies in near future. Symbiotic pacemakers, which achieving pacemaker energy requirement via converting biomechanical energy from the beating heart into electricity have become a favorite of researchers in recent years for cardiac pace makers and also for stimulators for nerve and muscle diseases.

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EEG based brain-computer interface control applications: A comprehensive review

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ABSTRACT

Brain computer interfaces (BCI) is a tool that can make user requests to computerized systems by directly processing brain signals. In order to perform the procedures to be performed, brain signals must be classified. For this purpose, many classification algorithms have been tried with machine learning. The purpose of this study is to talk about both the type of brain signals used in the brain computer interface and the machine learning techniques used in the classification of these signals. In addition, summary information about the classification methods used in brain computer interface control applications in recent years are given in a table.

Key words: Brain computer interfaces, EEG, machine learning, classification, mental control signals.

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Introduction

The brain computer interface (BCI) is the system that transforms, develops a system that measures central nervous system (CNS) activity into an artificial output and replaces the ongoing interactions between CNS and the external or internal environment. More simply, a BCI can be defined as a system that converts brain signals into new types of output [1]. The aim is to help people with serious disabilities to live their lives as regularly as possible. Some of these disabilities are classified as neurological neuromuscular disorders [2]. BCI helps neurological patients in daily life, but is generally used for purposes such as: medical, neuro-economic and smart environment, neuromarketing and advertising, education and self-regulation, games and entertainment, and security and authentication [3].

Many operations need to be performed to perform a command with the brain computer interface system. These processes will be mentioned below as articles. But in summary, the working principle of a brain computer interface is as follows in the block diagram in Figure 1: The signals received from the cortex by invasive or non-invasive methods are passed through pretreatments such as amplification and filtering. The signals are then subjected to feature extraction in order to reduce and convert them to data sufficient for classification. The data obtained from here are directed to the classifier according to the classification method whether it is trained or uneducated. In order to realize control in brain computer interfaces, the most accurate classification with the most accurate data is done by classification methods within the scope of machine learning. The purpose of this study is to examine the machine

learning methods used to classify the EEG signal types used in brain computer interface control applications in the last 5 years.

between neurons via electrodes over the scalp [5,6]. EEG is a type of biopotential amplifier that transfers the signal received through the

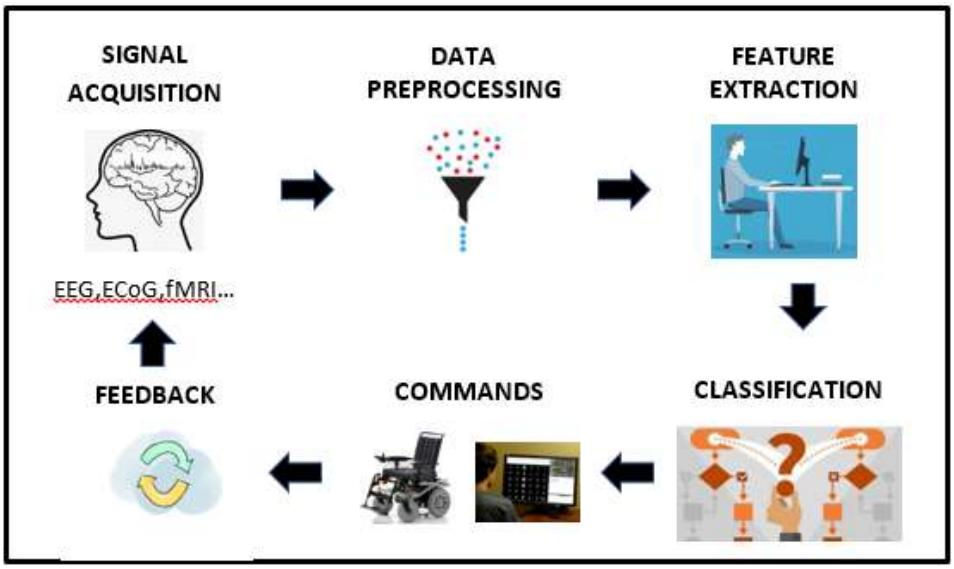

Figure 1. Brain computer interface block diagram.

Signal acquisition

The first thing to do in brain computer interfaces is to obtain brain signals. Many methods are used for this. These methods can be divided into two groups as generally invasive and non-invasive. Examples of invasive methods are ECoG, microelectrode arrays, while non-invasive methods are EEG, fMRI, fNIRS, MEG. In Table 1, there are signal acquisition methods used in brain computer interface technologies [2], [4].

EEG, which is one of the signal acquisition methods, is the most used method in brain computer interfaces due to its features such that it contains the least risks and difficulties during application due to its non-invasiveness, being more economical and portable than other methods. Therefore, this study focuses only on EEG. A graphic is cited from the work cited in Figure 2 [5].

Electroencephalography is the process of measuring and recording the postsynaptic potentials resulting from ionic activities

electrodes to the system output by subjecting it to amplification and filtering [7]. To perform these operations, as shown in the EEG block diagram in Figure 3, the signals received through the electrodes are amplified with the operational amplifier and filtered on the frequency axis, passed through the last amplifier, converted to digital and displayed for analysis according to the new function or directed to the new function.

Electrodes are placed on the scalp according to certain standards. The most common and traditional of these standards is the 10-20 electrode placement system designed by Jasper in 1958. In this form of settlement, the head is marked by four standard points. "Nasion", nose; "inion", the back of the head; left and right "Preauricular" means ear, dividing between "Nasion" and "inion" to be 10-20-20-20 and 10%, electrodes placed. Other electrodes are placed with these electrodes to form a circle [8]. Figure 4 shows the location points of the 10-20 electrode system.

Table 1. Signal acquisition methods used in brain computer interface technologies.

Signal Acquisation Method	Signal Source Type	Invasive/Non-Invasive	Spatial Resolution	Temporal Resolution	Portability
Electroencephalography (EEG)	Electrical	Non-invasive	~10 mm	~0.001 s	Portable
Electrocorticography (ECoG)	Electrical	Semi-invasive	~1 mm	~0.003 s	Portable
Magnetoencephalography (MEG)	Magnetic	Non-invasive	~5 mm	~0.05 s	Non-portable
Positron emission tomography (PET)	Metabolic	Non-invasive	~1 mm	~0.2 s	Non-portable
single photon emission computed tomography (SPECT or SPET)	Metabolic	Non-invasive	~1 cm	~10 s–30 min	Non-portable
Functional magnetic resonance imaging (fMRI),	Metabolic	Non-invasive	~1 mm	~1 s	Non-portable
Optical imaging (functional Near InfraRed (fNIR))	Metabolic	Non-invasive	~2 cm	~1 s	Portable
Intracortical Neuron Recording	Electrical	invasive	~0.1 mm	~0.003 s	Portable

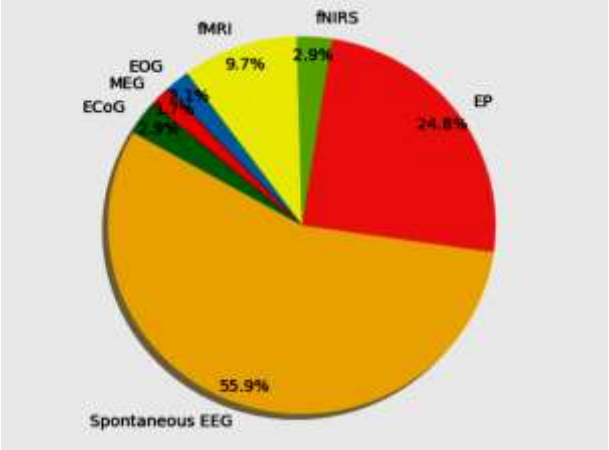

Figure 1. Usage rates of signal acquisition methods in the literature.

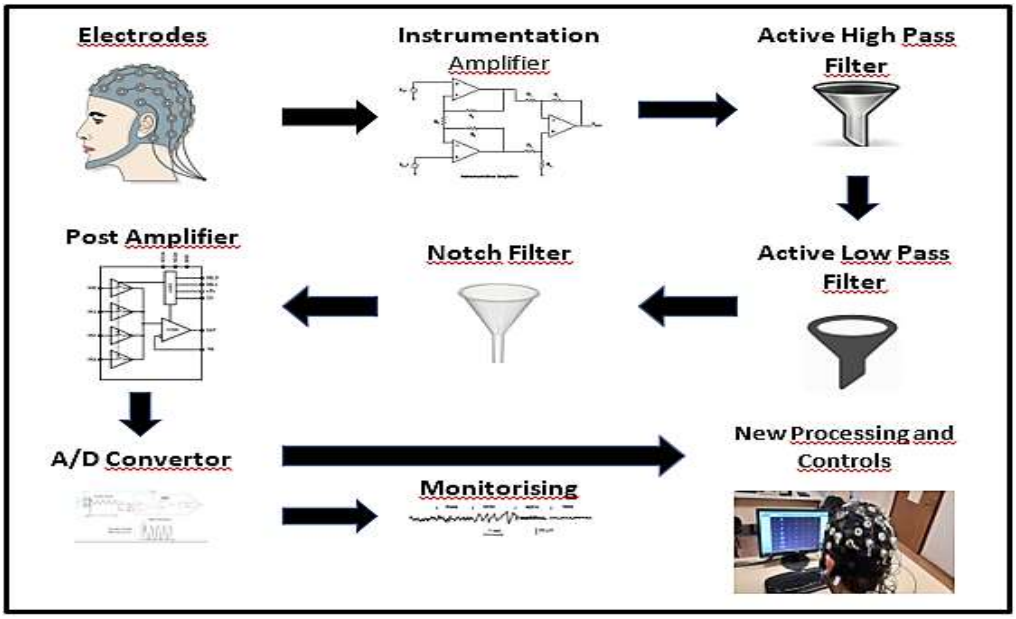

Figure 2. EEG block diagram.

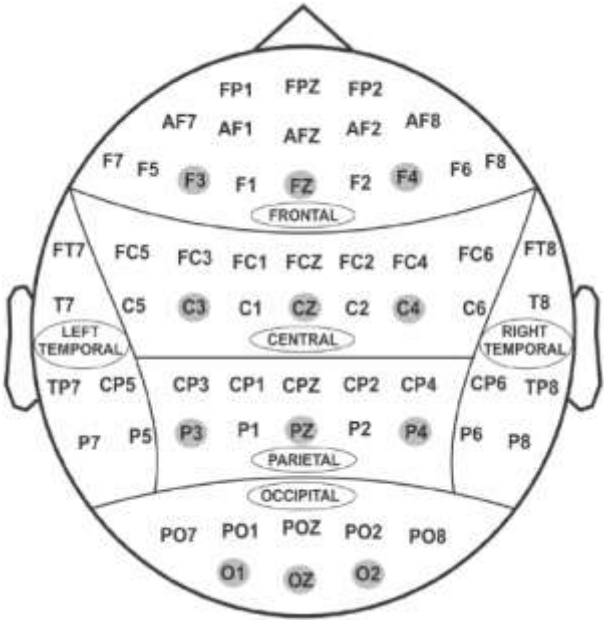

Figure 3. 10-20 elektrot sisteminin yerleşim noktaları [9].

In the use of EEG systems, a conductive gel or paste should be applied to bridge the gap between the scalp and the electrode and reduce the electrode impedance. However, with the development of dry electrodes, it eliminates the need for conductive gel or paste application, thereby reducing the electrode application time, allowing users to record EEGs for wired and wet electrode systems in impractical situations [10]. It has even been argued that EEG data recorded from a wireless dry electrode system can replace EEG data recorded with gel electrodes from a conventional system [11].

An EEG system should display a maximum of 6 µVpp input noise to detect µV level EEG signals. This nominal peak-to-peak noise can be converted to average square root (rms) noise, resulting in an integrated noise of 0.91 µVrms. As a result, state-of-the-art bioamplifiers target a <1 µVrms noise for the input, usually 0.5-100 Hz bandwidth. Also, 1 / f noises are typically reduced by dynamic circuit techniques [12]. Signals are filtered and amplified between these limits.

Signal processing

Since the ionic current is formed inside the brain, it is measured in the scalp, and layers between the cortex and the electrodes, such as the skull, reduce the Signal-to-Noise Ratio (SNR) by approximately 5%, which represents the relationship of the original brain signals to the measured EEG signals [13]. EEG recordings are often negatively affected by noise with different artifacts. Artifacts in the EEG recording are various species from different sources. Artifacts in EEG can originate from internal and external sources and mix noise into recordings in both temporal and spectral areas with broad frequency bands. Internal artifacts result from the patient's physiological activities (eg ECG, EMG / muscle artifacts, EOG) and movement. External artifacts are environmental interference, recording devices, electrode pop-up and cable motion.

In addition, some artifacts appear as regular periodic events, such as ECG or pulse (regular / periodic), while others may be extremely irregular. In order to increase the Signal-to-Noise Ratio (SNR), operations that will clear the signal from artifacts should be done. Cleaning the artifact involves canceling or correcting the artifacts without disrupting the corresponding signal. This is done primarily in two ways: filtering and regression, or separation / separation of EEG data into other fields. With regression analysis, Independent Component Analysis (ICA), Principal Component Analysis (PCA) or Morphological Component Analysis (MCA), Blind Source Separation, Wavelet Transform, Empirical Mode Separation, Adaptive Filtering or their hybrid use are used to clear the signal from artifacts [14].

Feature extraction

Feature extraction in brain computer interfaces means identifying information in domains other than brain signals that are free from noise. These properties can be signal amplitude, signal mean, kurtosis, variance in the time domain as well as Fourier transform and mean frequency in the frequency domain. Also, a feature that can be valid for both domains is the information extracted from the wavelet transform [15].

The result appears to vary significantly from feature to feature. Feature selection provides less data and hence the classification system becomes less complex and increases the calculation of machine learning algorithms [16]. That is, it is important in terms of cost, working time and performance of the system whether or not to use which features for classification in feature selection [17].

Feature selection is used not only to achieve the smaller size of the feature matrix for classification, but also to select a corresponding subset of all available features that throw out irrelevant features from the matrix, which can reduce noise. Some of the feature selection methods used for this feature reduction are: Principal Component Analysis, Linear Discriminant Analysis, Factor Analysis, Multi Dimensional Scaling, Isometric Feature Mapping, Complex Band Power, Common Spatial Patterns [18].

Classification

A classification is made according to the control application using the feature matrix obtained from the appropriate feature selection methods. Classification techniques are used to identify different brain signals produced by the user. These identified signals are then converted into control commands for application interface purposes [19]. Classification methods can be divided into two as supervised and unsupervised. Supervised classification is a traditional classifier where weights of optimum values are applied to the predictive states as supervised labels.

It is clear that the classification techniques based on supervised learning are largely preferred in the literature compared to those based on unsupervised learning. Unattended techniques are mainly used for feature selection. However, unsupervised techniques such as Gaussian mix models have been used for EEG classification problems other than MI EEG processing, and may possibly be applied to MI EEG in future studies [20]. Various machine learning algorithms have been used as emotion classifiers such as support vector machine (SVM), K-nearest neighbors (K-NN), linear separation analysis (LDA), random forest, Naïve Bayes (NB) and Artificial Neural Network (NB). Therefore, in general, the choice of which classification algorithm can be used when designing a BCI largely depends on both the type of encoded brain signal and the type of application being controlled [21]. Figure 5 shows a diagram describing the estimates made by supervised classification method.

The unsupervised classification is the classifier where an estimate is added to the system to determine possible target characters and train the classifier. For example, Kindermans et al. They proposed a method that uses expectation maximization (EM) to train the system during an unattended free writing session. During use, the subject selects characters for a target word or phrase as in the traditional system. After each election, the classifier tries to retrain himself using an iterative process. First, EEG signals are classified according to a random initial system configuration. Then, looking at these classifications as real tags, system parameters are optimized as in a training session. Using

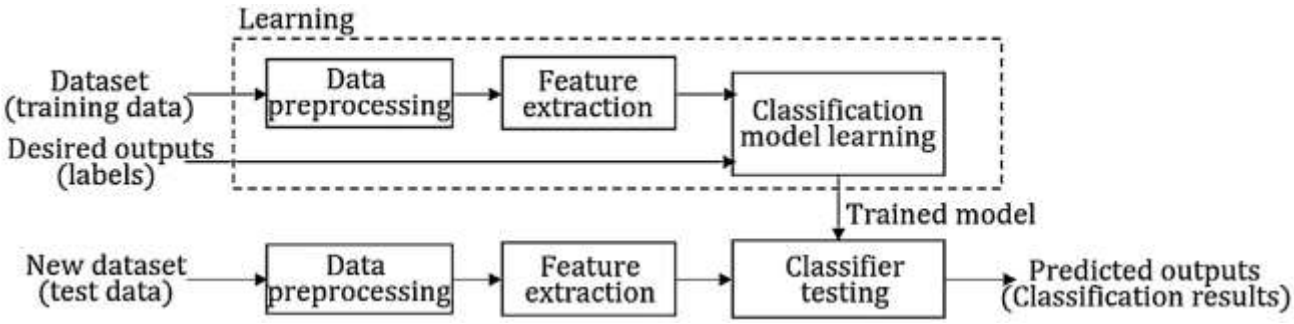

Figure 4. A diagram describing the estimates made by supervised classification method [22].

these parameters, EEG signals are reclassified and change alternately until the process gets close to a single configuration. This method depends on the initial configuration and may result in local optima that does not classify the signals correctly. In this study, the problem was solved by creating multiple initial configurations and running EM separately for each. The result with higher log probability will be selected as the true classifier [23],[24].

In recent years, classifiers have focused on identifying and designing classification methods that are compatible with the characteristics of EEG-based BCIs. In particular, topics such as low signal / noise ratio of EEG signals, which are the main challenges faced by classification methods for BCI, not being stationary over time, calibrating the classifiers with available training data of users' EEG signals, and eliminating overall low reliability and performance of existing BCIs. Adaptive classifiers have been developed in online applications to track changes in EEG features whose parameters are incrementally updated over time, i.e. to cope with EEG stability. Adaptive classifiers are also used to deal with limited training data by learning online, so less offline training data is required. Transfer learning techniques aim to transfer properties or classifiers from a single area. For this reason, they aim to address the non-stationary and limited educational data within the subjects by completing a small number of educational data that can be obtained with the data transferred from other fields. Finally, to compensate for the low EEG signal-to-noise ratio and poor reliability of existing BCIs, new methods for processing and classifying signals in one step were combined, combining feature extraction, feature selection, and classification. This was accomplished using matrix (especially Riemann methods) and tensor classifiers, as well as deep learning. The additional methods explored specifically aimed at learning with limited amounts of data and dealing with multiple class problems [25].

The types of EEG signal classified used in BCI

The purpose of this study is to investigate which classification method is widely preferred in EEG signal types used practically in brain computer interfaces. For this purpose, this section describes what type of EEG signals are used in BCI in practice.

In brain computer interface systems, control application is done by solving the meaning of thought. For this, it is necessary to detect and classify a brain signal pattern or the response expected from the brain for a specific task. EEG based BBA systems that can be used in practice are named according to the type of EEG signal used. The brain signals related to the event used in the brain computer interfaces in practice are: P300 signals resulting from the acquisition of potentials, steady state visual evoked potentials

and slow cortical potentials. The mental strategy that needs to be developed for these potentials to arise is to be focused on a certain stimulus. Cortical oscillations, on the other hand, are sensorimotor rhythms obtained from the sensory motor cortex of the brain, for example, with the imagination of a limb movement. For this reason, his mental strategy has been named as an engine dream [26].

BCI is based on control signals received directly from the brain. Some of these signals are relatively easy to remove and some are difficult and require some extra pretreatment. These control signals can be divided into three categories: Excited signals, Spontaneous signals and Hybrid signals [2]. It is showed in Table 2. We concentrated on the 4 most commonly used EEG signal types in practice among the 3 categories mentioned in this study: A Sensori Motor Rhythms (μ and β rhythms) based BBA systems. K Slow Cortical Potential (YKP) based BBA systems. 300 P300 Signal based BBA systems. Steady State Visual Evoked Potential based BBA systems. Table 3 contains summary information compiled from studies related to this subject.

Table 2. Mental control signals [2].

MENTAL CONTROL SIGNALS					
EVOKED		**SPONTANEUS**			**HYBRID**
SSEP signals are brain signals that are generated when the subject perceives periodic stimulus such as flickering image, modulated sound, and even when the subject feel some vibrations	**P300** It is an EEG signal that appears after almost 300 ms when the subject is exposed to infrequent or surprising task.	**Motor and Sensorymotor Rhythms** are those rhythms related to motor actions such as moving arms. These rhythms are coming from over the motor cortex with frequency bands located at μ (≃8–13 Hz) and β (≃13–30 Hz). The amplitude of these rhythms could be controlled by the subject.	**SCP (Slow Cortical Potentials)** is an EEG signal that belongs to a frequency below 1 Hz. It is a low frequency potential detected in the frontal and central parts of the cortex; it is also the results of the depolarization level shifts in the upper cortical dendrites.	**Non Motor Cognitive Tasks** Non-motor cognitive tasks mean that cognitive tasks are used to drive the BCI. Many of the tasks could be performed such as music imagination, visual counting, mental rotation, and mathematical computation	Hybrid signals mean that a combination of brain generated signals are used for control. Therefore, instead of only one type of signals is measured and used in the BCI system, a hybrid of signals are utilized. The main purpose behind using two or more types of brain signals as input to a BCI system is the reliability and to avoid the disadvantages of each type of signals.

Table 3. Information from some studies on brain computer interface in recent years

Source	EEG Signal Types	Classification Methods	Application	Accuracy	Subject Type	Preprocessing	Feature Extraction Method
[27]	P300	PCA	P300-based text editor for Android-based devices	97.19	Healthy	Common average reference spatial filte	PCA
[28]	P300	LDA eSVM CNN-1 MCNN1 EFLD SRDA STDA HODA+LDA SWLDA	Defining tensor-based feature reduction technique Higher Order Spectral Regression Discriminant Analysis (HOSRDA)	LDA 96.5 eSVM 96.5 CNN-1 94.5 MCNN1 95.5 EFLD 95 SRDA 95 STDA 95 HODA+LDA 94 SWLDA 92.5 Reg. + HODA+LDA 92	Healthy (Data of BCI competition III)	Bandpass filtered in the band 0.1–60 Hz Each trial was bandpass filtered between 0.1 and 10 Hz with 8-order Chebyshev type I filter and then decimated to 20 Hz	HOSRDA
[29]	P300	LDA	Impact of fatigue brain behavior on P300 signals and developing wavelet multiple solution complex network to analyze P300 EEG signals	95.42	Healthy 10	The signals are filtered with a bandpass of 1–40 Hz. The Independent Component Analysis (ICA) method is applied to remove eye movement and blink artifacts.	-
[30]	P300	Naïve-Bayes	Designing an interface for social attention disorders such as autism spectrum disorder using Virtual Reality	Between 85-90	13 Healthy 4 autism spectrum disorder	Notch: 50 Hz; 2Hz–30 Hz, 8th order Butterworth band-pass filter	FC filter model Max-SNR filter model spatial filtering
[22]	P300	SVM	In P300 spells, based on the distance of each row and column according to the targeted character, separating the training data into groups at the same distance, measuring the accuracy rate in the eSVM classifier, examining its effect on the classifier diversity.	97	Healthy (Data of BCI competition III)	Bandpass frequency filtering between 0.1 and 10 Hz	eSVM

[31]	P300	SVM	An approach based on multipurpose dual differential evolution (MOBDE) algorithm to optimize system accuracy and number of EEG channels used for classification	92.8 (averaged)	Healthy	A band-pass filter of cut-off frequencies between 1 and 10 Hz	down sampling
[32]	P300	SWLDA, FLDA	To apply the vibration movement with piezo activators to the fingers in the Oddball paradigm method, to ensure the formation of P300 and to use for the classification of 2 and 4	2 class. 85 4 class. 60	Healthy	band-pass filtered from 0.53 to 120 Hz	moving average and down sampling
[33]	P300	SVM	Classification of schizophrenia patients and healthy individuals using both sensor level and source level features extracted from EEG signals recorded during an auditory oddball task	88.24	34 Schizophrenia 34 Healthy	band-pass filtered at 1 to 30 Hz	sensor-level features Source level features the combined features
[34]	P300	SVM	Three distinctive feature-based multi-core learning (MKL) is recommended to learn an efficient P300 classifier to improve character recognition accuracy in a P300 speller BCI.	98	Healthy	4th-order bandpass Chebyshev Type I between 0.1 Hz and 20 Hz.	the three discriminant features: Raw samples Amplitude Negative area
[35]	P300	BN (Type of CNN)	Develop a new CNN called BN (Batch Normalization) to detect P300 signals	84	Healthy	8th-order bandpass Butterworth filter 0.1 and 20 Hz.	CNN
[36]	P300	SVM	To design a new lie detection system and apply 2 new feature extraction methods in the system	88.7	Healthy	band pass at 0.01 Hz to 100 Hz ocular artifact reduction	Wavelet packet transform Nonlinear interdependences
[37]	P300	Unsupervised	Collection of matching filter and context analysis for P300 detection, use of unsupervised learning systems	91.66	Healthy (physionet. org)	Band-Pass Filtering 0.15 Hz and 5 Hz cancel the saccadic spike poten- tial (SP) ICA Wiener filtering	-
[38]	P300	LDA	To evaluate the somatosensory discrimination and command after using the vibrotactile P300-based Brain-Computer Interface (BCI) in Unresponsive Vigilance Syndrome (UWS) and to investigate the predictive role of this cognitive process on clinical outcomes.	97	Thirteen UWS patients and six healthy	The data were notch-filtered at 50 Hz and bandpass-filtered within 0.1–30 Hz. Trials with an amplitude above 100 mV were automati- cally rejected.	-

[39]	P300	LDA	The auditory paradigm, also known as the drip-stimulating hearing BCI paradigm, the audio paradigm (BP), called drip paradigm (BP), was compared with the difficulty and difficulty scores to demonstrate the advantages of online accuracy and DP.	80.87 (averaged)	Healthy	filtered with a third-order Butter-worth band-pass filter between 0.1 and 30 Hz.	
[40]	P300	LDA	The effect of the translucent face model (STF-P) (the subject could see the target character when flashing) and the traditional face model (FP) (the subject could not see the target character when flashing) Performance comparison in terms of transparency in terms of transparency	95.2	Healthy	Band-pass filtered 0.5-30 Hz	Downsampli ng Winsorizing
[41]	MI	SVM	Examination of EEG signals of 4 different states Turning hands on or off with the audio video command Open and close hands with silent video Pressing the piano with the same two ways command	87.5	Healthy	band-pass filtered from 0.5 to 40 Hz common average reference visual in- spection	Common Spatial Pattern (CSP) filter
[42]	MI	Naive Bayes	A correlation analysis was performed between various quantitative evaluation metrics of motor imageries. For this, the actions to be done by the subjects were taught in the first step, the most effective image strategy was determined in the 2 and 3 steps.	87 (ortalama)	Healthy	bandpass filtered in 4– 40 Hz range with a 4th-order Butterworth filter,	Common Spatial Pattern (CSP) filter
[43]	MI	Linear Regression	Design a system to modulate activity in the default mode network (DMN) without involving sensorimotor paths by instructing to activate their reference memories or focus on a process without reminder content.	ALS 60.8 Healthy 62.5	11 Healthy and 5 ALS	ICA	computed the trial-wise log-bandpower of the averaged, combined y- and a-range at every channel location using the Fourier transform.
[44]	MI	LDA	30 healthy SMR-BCI participants were trained to control right hand movement and SMR-based BCI on separate days for five days with traditional bar feedback (CB) or visual funnel feedback (UF) or multimodal (visual and auditory) funnel feedback (MF).	63	30 healthy		power spectral density (PSD)

[45]	Hybrid P300-SSVEP	SSVEP-> canonical correlation analysis (CCA) P300 -> SWLDA	The hybrid spelling consists of nine panels that vibrate at different frequencies. Each panel contains four different characters that appear in a random order. The vibrating panel and the periodically updated character evoke the dual-frequency SSVEP, while the strange stimulus of the target character evokes the P300.	SSVEP 89 P300 90 Hybrid 93	Healthy 10	band-pass-filtered at [2 50] Hz	
[46]	mVEP	SVM	A red line sliding to the left in random order appears in each of the 6 stimuli placed in a rectangular visual interface. Contribution of using deep learning to the classification in the selection of objective features	Compressed sensing and deep learning features 87.5 Conventional mVEP features 84.0	Healthy 11	50 Hz notch filter bandpass filtered within 0.5–10 Hz	Deep learning
[47]	SCP	MLP	Each signal is first divided into wavelet sub-marks, and then features such as Logenergy entropy are extracted from these sub-marks. These features are fed to an MLP for classification. Finally, it was compared with SVM and KNN.	MLP 92.83 KNN 89.76 SVM 86.01	BCI Comp. 2003 datasets		Wavelet packet decomposition (WPD) Log energy entropy

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Journal of Bionic Memory **Review article**

Technological devices in treatment of diabetes mellitus

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ABSTRACT

Technological inventions are being used recently to enable the treatment of diabetes mellitus more effective and easier to comply. Insulin pumps, after the implementation of readily available insulin pens, have made the transition to a very important stage in diabetes therapy. Insulin pumps have also enabled the transition from intermittent injection patterns to treatment modalities that provide continuous insulin infusion in diabetic subjects. Remedial studies on the next stage, the artificial pancreas, are still ongoing. Each of these treatments has its own advantages, some difficulties, and safety issues. We aimed to discuss the features of insulin pump devices in present short review.

Key words: Diabetes mellitus, insulin pump, therapeutics, insulin infusion systems, technological devices.

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Introduction

Insulin therapy is needed to ensure glycemic control in all patients with Type 1 diabetes mellitus (DM) and many Type 2 DM patients, and daily multiple-dose insulin treatment is usually required in the later stages of the disease [1]. Daily multiple dose insulin treatment is a difficult regimen to apply for certain diabetic subjects, thus well glycemic control cannot be achieved in these individuals [2]. The idea of providing continuous insulin infusion via an insulin pump has emerged in order to provide treatment compliance and better blood glucose control. The first insulin pump was tested on patients with Type 1 DM in 1976, and researchers were concluded that this treatment could provide physiological glucose concentration in blood of the diabetic patients [3]. While the insulin pumps produced at that time were the size of a backpack, their size was reduced to the size of a cell phone currently. Insulin pump has become a much more frequently and effectively used treatment option in diabetes mellitus during last 35 years, the method owing to the developing computer technologies and new analog insulins [4]. The rate of insulin pump use as a treatment modality varies from country to country which depends on the differences in health and insurance systems. While about 64% of Type 1 DM patients in the United States treated with an insulin pump [5], this rate rises to 70-93% in certain centers in Europe [6]. These rates are predicted to increase in the future as technological advances in diabetes therapy evolve in the following years.

Types of insulin pumps

Patch and micro insulin pumps: These pumps are smaller in size than conventional insulin

pumps. It consists of two parts; the first part is both electronic and mechanical part, which is the insulin reservoir connected to the skin with a short cannula, and the other is the electronic part that enables the control of insulin release with a wireless connection [7]. While some of this pump type provides bolus therapy in addition to the programmed basal insulin infusion, some of them, which are frequently used for Type 2 DM patients, do not allow a programmable basal infusion release, and give fixed bolus doses [8]. There are contradictory results in studies on this type of insulin pumps. In addition to studies showing that there was no difference in HbA1c levels when using different types of pumps in patients using daily multi-dose insulin therapy [9], other studies observed a significant improvement in HbA1c levels and a decrease in the required daily insulin dose and the rate of hypoglycemia after switching the treatment to the patch insulin pump [10].

Sensor integrated insulin pumps: While there is no increased risk of hypoglycemia in many studies in adult patients using insulin pumps, there are studies showing that the risk of hypoglycemia increases in the pediatric age group [11]. Based on this, the idea of integrating a continuous glucose monitoring system into insulin pumps has emerged. When these devices detect hypoglycemia, they automatically stop insulin infusion. It has been shown that a better glycemic control is provided with less risk of hypoglycemia with this type of insulin pump [12]. While it reduces the risk of hypoglycemia, it does not protect against hyperglycemia, hence this is the disadvantage of this type of insulin pumps. Therefore, the idea of an artificial pancreas has been put forward.

Dual hormone closed loop system (Artificial pancreas): Glucagon is released from pancreatic alpha cells in response to hypoglycemia in healthy individuals. This protective mechanism may not be activated in patients with type 1 DM and susceptibility to hypoglycemia increases even in cases that insulin secretion is interrupted. Dual hormone closed-loop systems aim to better mimic this physiological process by directing both insulin and glucagon release and by releasing glucagon when hypoglycemia is occurred or predicted [13]. There are some obstacles to widely use of dual hormone systems, such as the need for a double chamber infusion pump and the lack of stable glucagon formulations [14]. Studies on this system have shown that this system provides better glycemic control compared to the other insulin pump devices, although these studies involve small population and short-term follow up [15,16].

Traditionally dual hormone approach has included the addition of glucagon, but different studies are currently testing the addition of pramlintide with insulin alone or with insulin and glucagon. Other adjunct therapies, such as glucagon-like peptide-1 and sodium glucose co-transporter-2 inhibitors used in conjunction with advanced algorithms, also have the potential to improve postprandial glucose control compared to existing artificial pancreatic systems. Each of these therapies which recommended as addition to the closed loop systems, have their own advantages, difficulties and safety problems [17].

Comparison of insulin pump and intensive insulin therapy

The DCCT (Diabetes Control and Complications Trial) study has shown reduced micro and macrovascular complications in 1441 patients with type 1 DM whom provided tight glycemic control by intensive insulin therapy or an insulin pump for 6.5 years,

compared to patients received conventional therapy [18]. The EDIC (Epidemiology of Diabetes Interventions and Complications) study showed that when patients in the DCCT study were followed for diabetic complications for 30 years, tight glycemic control also reduced micro and macrovascular complications in the long term [19]. In the same period, many studies showed that frequent and severe hypoglycemia increased cardiovascular morbidity and mortality by causing proinflammatory, prothrombotic effects and endothelial dysfunction [20]. After studies revealed that insulin pump therapy provides better HbA1c reduction with a lower risk of hypoglycemia compared to multiple injection therapy in type 1 DM patients, the use of insulin pumps has started to increase worldwide [10]. However, randomized controlled studies for Type 2 DM patients did not yield satisfactory results as they did in Type 1 DM patients. In a study by Raskin et al., which included 132 patients, a similar decrease in HbA1c was observed in both groups when the daily multi-dose insulin treatment was compared with insulin pump. However, at the end of the study, 93% of the patients using insulin pumps stated that they would prefer to use an insulin pump instead of previous insulin treatments due to ease of use, comfort and flexibility in treatment [21]. In another randomized controlled study by Herman et al., in which the insulin pump and multiple insulin injection treatments were compared on 107 patients, including those aged 60 years and above, a nonsignificant decrease in HbA1c was observed. Unlike the previous study, there was no significant difference between treatment satisfaction in both groups, and at the end of that study, the HbA1c levels of both groups were below 7%, unlike the study conducted by Raskin et al. [22]. In addition to these studies, there are reports showing that the insulin pump reduces HbA1c more effectively, but both the number of patients in these studies were less than the previous studies and the designs of the studies were different [23]. Globally, the use of insulin pumps for type 2 DM is considered in patients whose blood glucose levels were not well controlled with daily multiple dose insulin therapy.

Indications of insulin pump treatment

Inadequate glycemic control despite use of daily multiple dose insulin therapy in patients with type 1 DM [24,25];

- Pronounced Dawn phenomenon, severe insulin sensitivity
- Frequent episodes of severe hypoglycemia or insensitivity to hypoglycemia
- Brittle diabetes (including recurrent diabetic ketoacidosis episodes)
- Patients whose lifestyle requires flexibility (shift workers, long-distance drivers, etc.)
- Patients planning pregnancy but not achieving the targeted level of glycemic control before pregnancy

For type 2 DM patients [24,25];

- Patients under insufficient glycemic control despite regular follow-up under basal-bolus therapy
- Dawn phenomenon
- Patients with severe insulin resistance (patients required 500 units of insulin daily)

Contraindications of insulin pump treatment

Regardless of the type of diabetes mellitus, patients who are thought to be unable to provide the expected glycemic control with insulin pump can be summarized as follows [24,25];

- The subjects who do not want or are not able to measure fingertip glucose 3-4 times a day.
- Patients with a low level of education and low motivation to learn carbohydrate counting

- Patients with severe psychiatric disorders (psychosis, severe anxiety, depression, etc.)
- Patients who are concerned that the use of insulin pumps may affect their lifestyle (contact sports, patients who think it will affect their sex life, etc.)
- Patients with unrealistic expectations about the insulin pump

Insulin pump and pregnancy

Insulin resistance increases as the week of gestation progresses with the effects of human placental lactogen, cortisol and prolactin. The need for insulin increases 2-3 folds as the gestational and pregestational diabetic patients approach to the end of pregnancy. These physiological changes cause a predisposition to ketosis during the fasting period (especially in the early stages of pregnancy) and to hyperglycemia during postpartum (especially in the later stages of pregnancy) [26].

The positive effect of insulin pump on glycemic control during pregnancy has not been clearly established. In a meta-analysis of 307 patients in which randomized controlled trials were evaluated, no superiority of the insulin pump over daily multi-dose insulin was observed [27]. In another retrospective study, it was reported that diabetic ketoacidosis and neonatal hypoglycemia were observed more frequently in patients using insulin pumps during pregnancy compared to the patients received daily multiple dose insulin [28]. Therefore, patients using insulin pumps during pregnancy should be warned about technical problems related to the pump, intensive training should be given to the patients and the patient should be followed closely.

Complications of insulin pump

Several complications are associated with insulin pump treatment due to mechanical failure of the pump, set or injection port. These complications have been reported at rates varying around 45% to 84% in different studies [29,30]. The risk of developing diabetic ketoacidosis and glycemic fluctuations increase during pump failure since insulin infusion is interrupted. Another complication is skin reactions such as infections at the infusion site, bruising and itching. In addition, lipohypertrophy may develop in the infusion area and this picture disrupts glycemic control [31]. The most important way to avoid these complications is providing adequate pump training to the patients, teaching the patient how to solve those mechanical problems, and to explain how to start subcutaneous insulin therapy in cases where the pump is failed.

Conclusion

Insulin pump would be one of the main treatment options in patients with diabetes mellitus in the near future. The use of insulin pumps will become widespread with technological advances which will reduce their complications and increase their efficiency.

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